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ARCHIVES of INTERNAL MEDICINE

VOLUME 66 JULY 1940 NUMBER 1

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STAPHYLOCOCCIC SEPTICEMIA

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The diagnosis of staphylococcic septicemia brings to many minds a well grounded fear as well as a feeling of unfortunate hopelessness. This hopelessness is an unhealthy condition, often leading either to procrastination with the loss of life-saving time or to the waste of valuable therapeutic agents because of inadequate dosage. The fear, however, together with a healthy stimulation of ingenuity, is undoubtedly praiseworthy. It should not only produce an increase in early recoveries together with a decrease in cases of chronic osteomyelitis, but it should also encourage scientific workers to renewed efforts in discovering more efficient and more specific means of treatment. When this is done there will be a reduction in the exceedingly high mortality.

MORTALITY

The mortality, as observed in statistics of staphylococcic septicemia, varies greatly. In 1936 MacNeal and Frisbee [1] reported a death rate of 75 per cent for a series of 100 patients of all ages treated by bacteriophage. Rosenow and Brown [2] reported a rate of 66 per cent for a series of patients seen between 1934 and 1936. Mendell,[3] in reviewing the reports on a series of 35 patients having the disease between 1929 and 1937, found 29 deaths, or 83 per cent. In 1939 Stookey and Scarpellino [4] gathered reports on a series of 177 patients treated by various means, with a death rate of 91.4 per cent, while of 17 patients whom they treated with staphylococcus antitoxin they lost 9, or 53 per cent. This last figure corresponds closely with the figures reported by

From the Cowell Memorial Hospital, University of California, Berkeley.

1. MacNeal, W. J., and Frisbee, F. C.: Am. J. M. Sc. **191**:179 (Jan.) 1936.

2. Rosenow, E. C., and Brown, A. E.: Proc. Staff Meet., Mayo Clin. **13**:89 (Feb. 9) 1938.

3. Mendell, T. H.: Staphylococcic Septicemia: Review of Thirty-Five Cases with Six Recoveries, Twenty-Nine Deaths and Sixteen Autopsies, Arch. Int. Med. **63**:1068 (June) 1939.

4. Stookey, P. F., and Scarpellino, L. A.: South. M. J. **32**:173 (Feb.) 1939.

Dolman,[5] one of the pioneers of treatment with antitoxin. The death rate which he reported as early as 1934 was reduced to 55 per cent by the use of antitoxin.

Encouraging results from the use of antitoxin and immune blood have prompted this report on patients with staphylococcic septicemia who were encountered by the staff at the students' health service of the University of California. The series extends over a period of thirty years, from 1909 to 1938 inclusive. Only those patients are included who manifested initial carbuncles, furuncles or blisters, together with positive blood cultures and other evidence of grave infection. There was a total of 7 such patients. Of these, 2, or 28.6 per cent, died. The only patient treated prior to the use of antitoxin died. Of the 6 treated since 1937 with large doses of antitoxin, only a single patient, or 16.7 per cent, died.

Data on Seven Patients with Staphylococcic Septicemia

Case	Age	Sex	Primary Focus	Day of First Positive Blood Culture	Specific Treatment			Days in Hospital	Result
					Antitoxin, Units	Immune Blood, Cc.	Toxoid, Cc.		
1926	20	♂	Furuncle	2	None	...	...	4	Death
1937	20	♂	Blister	3	460,000	...	...	24	Recovery
1938	18	♀	Furuncle	1	630,000	480	...	53	Recovery
1938	18	♀	Furuncle	7	340,000	100	...	19	Recovery
1938	21	♂	Furuncle	5	340,000	...	1.9	40	Recovery
1938	22	♂	Furuncle	12	1,080,000	...	...	36	Death
1938	23	♂	Blister	5	740,000	535	1.9	92	Recovery

INCIDENCE

Although the death rate among patients with an infection of the blood stream with the staphylococcus has been so high, it is interesting and encouraging that the occurrence of the disease is comparatively infrequent when compared with the great number of patients with superficial infections, such as carbuncles and boils. This series of 7 patients with septicemia was observed during the thirty year period among a total of 11,568 patients with carbuncles, boils and blisters, or at a rate of 6 patients with septicemia per 10,000 of the total number having superficial infections. Although the percentage of superficial infections was much lower in women than in men, the percentage with staphylococcemia was equal in the sexes. All of the patients in this series were within the limits of 18 to 23 years of age. There were 2 girls and 5 boys. Other interesting facts are found in the accompanying table.

5. Dolman, C. E.: (*a*) Canad. M. A. J. **30**:601 (June) 1934; (*b*) **31**:1 (July) 1934; (*c*) **31**:130 (Aug.) 1934.

CLINICAL COURSE AND COMPLICATIONS

All of the patients had irregular septic temperatures, the highest point varying from 39 C. (102.2 F.) to 42.5 C. (108.5 F.). Leukocytosis was present in all the patients, the white cell count varying from 10,700 to 41,000 in most of the patients. Three of the 7 patients, or 43 per cent, had bilateral bronchopneumonia. One of these patients died. A pure culture of Staphylococcus aureus was recovered from the urine of 2 patients. One of these patients died, and autopsy revealed a cloudy swelling of the kidneys. A third patient showed a transient hemorrhagic nephritis, which completely cleared. Osteomyelitis was found in 2 patients. Roentgen examination revealed it in 1 patient who recovered, and in the other it was proved at autopsy. Multiple superficial pustules and deep abscesses occurred in 1 patient who died. Pure Staph. aureus was recovered from an infection of the umbilicus in 1 patient.

TREATMENT

The treatment consisted of surgical, supportive and specific measures. Surgical treatment with adequate drainage of the primary infecting focus was instituted. The only patient to die among those receiving antitoxin showed multiple abscesses. These were located over the right sacroiliac and the left sternoclavicular joints, in the superficial tissues of the left infraclavicular area and in the superficial and deep tissues of the left side of the neck. All abscesses were freely drained. The supportive measures consisted of careful nursing, of a well balanced and adequate caloric intake and of care of the water balance, with intravenous injection of fluids and transfusions of whole blood when indicated. For specific treatment, there were used for all patients since 1937 early and large doses of staphylococcus antitoxin.[6] The total individual dose ranged from 340,000 to 1,080,000 units and was given intramuscularly. In 3 patients immune blood was injected intramuscularly. The only patient of the group to die after being treated with antitoxin did not receive any immune blood. The immune blood was whole blood containing bacterial antibodies from donors who had been immunized by injections of undenatured staphylococcus antigens, as recommended by Dr. A. P. Krueger, professor of bacteriology at the University of California. Two patients received 1.9 cc. of toxoid[6] during their convalescence.

6. All the antitoxin and toxoid used for these patients was from the Lederle Laboratories.

There are two outstanding theories of immunity to the staphylococcus. According to one theory, immunity is due to the amount of antitoxin in the tissues. Burnet [7] demonstrated in 1929 that certain strains of the staphylococcus produce a virulent exotoxin. Branch [8] summarized the five proved effects of exotoxin on the various tissues of the body. These are as follows: hemolysis of the erythrocytes due to hemolysin, destruction of the leukocytes by leukocidin, necrosis of tissues, coagulation of the blood plasma by the coagulase and, finally, death due to the lethal element. If treatment is to be effective, the first theory is that there must be sufficient antitoxin present to prevent tissue change by these toxic elements. As the natural antitoxin content varies greatly and is frequently absent, treatment to be effective must early supply sufficiently large quantities of antitoxin. Advocates of the second theory maintain that immunity is due to the content of bactericidal and phagocytic elements in the tissues and in the cells. As these elements are not present in antitoxin they must be supplied by other agents, such as immune blood, or by chemotherapeutic substances, possibly of the nature of sulfapyridine. As this agent was not available during the treatment of the patients in this series, immune blood was used in the treatment of 3 patients.

REPORT OF CASES

CASE 1.—A 20 year old white youth entered the hospital complaining of a boil in one nostril and an elevated temperature. A blood culture was positive for Staph. aureus on the second day. Symptoms of meningitis appeared, but on examination it was observed that the spinal fluid was normal. The temperature rose steadily from 38.5 C. (101.3 F.) to 41.4 C. (106.5 F.). The patient died on the fourth day. Treatment was symptomatic.

CASE 2.—A white youth aged 20 entered the hospital complaining of pain in the right hip which excluded all motion of the leg. Two weeks previously he sustained blisters of the feet, which became infected. Three days before entry he had chills, fever, sweats and vomiting. Physical examination revealed (1) tenderness over the right iliac crest and to the right of the umbilicus, pain in both instances being referred to the right sacroiliac region, but no tenderness over the joint; (2) old blisters on the soles of both feet, and (3) a temperature of 38.8 C. (101.8 F.). Laboratory reports showed that the urine, which on the patient's entry had a white blood cell count of 1 to 3 and a red blood cell count of 50 to 80, was entirely normal in twelve days. Examination of the blood showed that during the acute sickness the white cell count ranged from 8,050 to 26,200. The count of the nonfilamented leukocytes, which was as high as 63 when the infection was severest, varied from 43 to 23 for a week after antitoxin was dis-

7. Burnet, F. M.: J. Path. & Bact. **32**:717 (Oct.) 1929.
8. Branch, A.: Canad. M. A. J. **39**:391 (Oct.) 1938.

continued and the patient well on the way to recovery. Blood cultures were positive for Staph. aureus on the first, second, third and fifth day but were negative thereafter, on seven examinations. Roentgenograms of the right sacroiliac joint taken two weeks after entry showed a pathologic condition of the right sacroiliac joint, with considerable osteomyelitis of the adjacent bone. Beginning two days after admission, when the first positive blood culture was reported, the patient received a total of 460,000 units of staphylococcus antitoxin in eight days. The temperature varied from 37.5 C (99.6 F.) to 40 C. (104 F.). The patient was dismissed to his home in twenty-five days. Four days later a thrombophlebitis appeared in the left leg, which caused some inconvenience for a few weeks. Roentgenograms of the right sacroiliac joint taken nine months after onset showed complete restoration of the joint with increased calcification of the surrounding bony tissues. Recovery was complete.

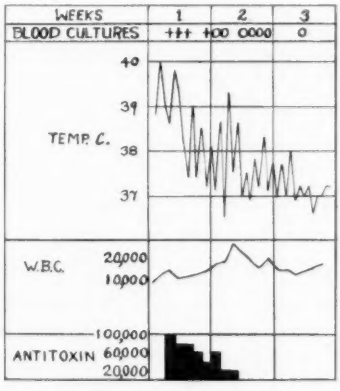

Chart 1.—Data on case 2.

Case 3.—A white youth aged 22 entered the hospital complaining of severe pain in the right sacroiliac region and of an elevated temperature and malaise of four days' duration. He gave a history of having had a boil on his right wrist twelve days before entry. Physical examination revealed only a small draining boil on the right wrist, tenderness in the right sacroiliac region and a temperature of 37.5 C. (99.5 F.). Laboratory reports indicated that the urine, which was normal for two weeks, began to show a trace of albumin and occasional red and white blood cells, and by the nineteenth day the urine showed a pure culture of Staph. aureus. Examination of the blood revealed that the red cell count ranged from 3,500,000 to 3,900,000 and the white cell count from 10,000 to 34,200. Blood cultures were negative from the time of the patient's entry until the eleventh day, when Staph. aureus was recovered. They again became negative after the administration of 400,000 units of antitoxin, but after further progress of the disease they became positive until the patient's death. Roentgenograms showed no abnormality of the sacroiliac joint, of the lumbar spine or of the sternoclavicular joint. Films taken two days before death showed a number of small scattered abscesses of the lungs and a retropharyngeal abscess.

Because of the history of a furuncle, sacroiliac pains and elevated temperature, although blood cultures were repeatedly negative until the eleventh day, the administration of antitoxin was started on the eighth day. On the eleventh day, the day on which the first positive blood culture was obtained, an abscess of the right sacroiliac joint was drained. On the fourteenth day, when the patient received the last dose of the first 400,000 units of antitoxin, the white cell count was 22,600, with 42 filamented and 42 nonfilamented leukocytes. On the next day the white cell count was 24,750, with 72 filamented and 16 nonfilamented leukocytes. This shift toward the right, together with a general improvement and four negative blood cultures, was deceiving. On the seventeenth day an inflammation began in the region of the left sternoclavicular joint and spread to the chest wall, to the neck and to the retropharyngeal space. For multiple abscesses which formed, numerous incisions were made. Although an additional 680,000 units of antitoxin was given, making a total of 1,080,000 units, the patient died on the

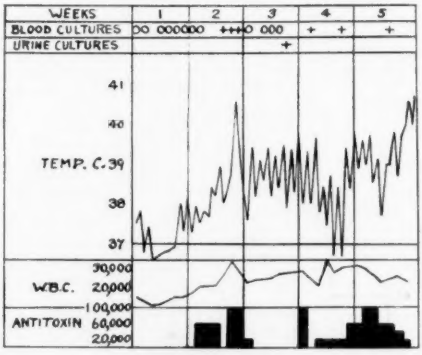

Chart 2.—Data on case 3.

thirty-fifth day. The diagnosis made at autopsy was multiple staphylococcic abscesses of the neck, the retroesophagus, the retropharynx, the left sternoclavicular and the right sacroiliac joint; multiple abscesses of the skin; bilateral bronchopneumonia with multiple septic infarcts; bilateral acute adhesive pleuritis; acute myocardial degeneration; acute hepatitis; acute splenitis, and cloudy swelling of the kidneys.

Case 4 (permission of Dr. Ruby L. Cunningham).—A white girl aged 18 entered the hospital complaining of a furuncle over the right eye of four days' duration, accompanied by fever. Physical examination revealed only a large furuncle with edema and redness of the forehead above the right eye, marked edema of the right eyelids and a temperature of 39.8 C. (103.6 F.). Laboratory reports showed the urine to be normal at all times. Examination of the blood showed a white cell count ranging between 8,000 and 21,000 during the illness. Blood cultures were positive for Staph. aureus on the second and fourth days. The administration of antitoxin and immune blood, which was started on the

second day, was continued until the twenty-ninth day because of bilateral bronchopneumonia manifesting itself on the ninth day. No other complications occurred. The temperature varied from 36.6 C. (98 F.) to 40.6 C. (105.2 F.). A total of 630,000 units of antitoxin and 480 cc. of immune blood was given. Recovery was complete.

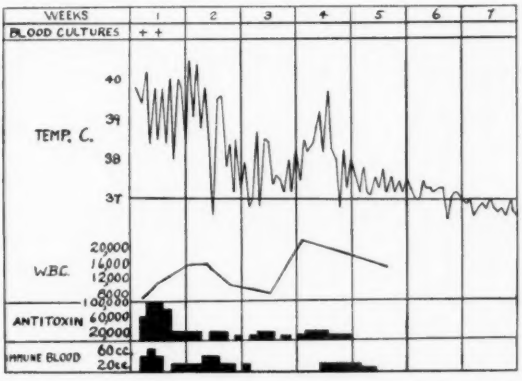

Chart 3.—Data on case 4.

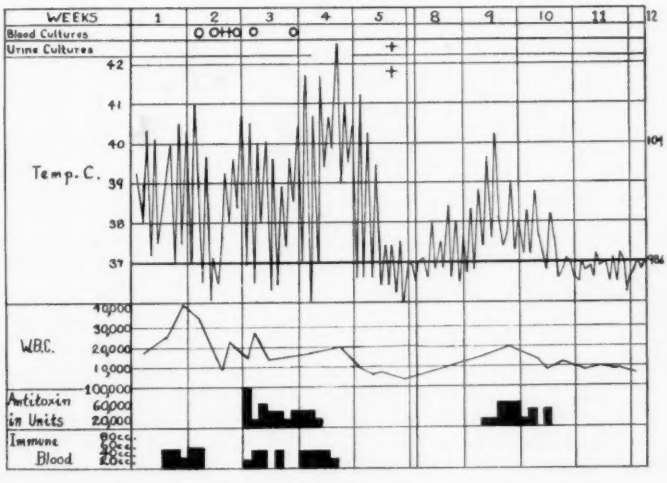

Chart 4.—Data on case 5.

CASE 5.—A white youth aged 23 entered the hospital complaining of severe sore throat, anorexia, nausea, chills and fever. Three weeks before he thought that an insect had bitten his left ankle. The extreme itching caused him to scratch the area, with two pustules resulting. The pustules healed, but two days before his entry to the hospital an inflammation started at the umbilicus. Physical

examination gave negative results except for an elevated temperature, a reddened pharynx, slight cervical lymphadenitis, inflammation of the umbilicus and two small healed scars on the inner aspect of the left ankle. Laboratory examination of the urine revealed that it remained normal until the thirty-fifth and thirty-sixth days, when pure cultures of Staph. aureus were obtained. Examination of the blood showed that the white cell count varied between 9,350 and 41,500 during the first and severest episode; it then dropped as low as 3,500 between episodes and varied again between 10,200 and 19,600 during the second episode. Blood cultures were positive for Staph. aureus on the twelfth and thirteenth days. Umbilical cultures were positive for Staph. aureus on the tenth day. Roentgenograms of the chest taken on the thirty-second day showed bilateral bronchopneumonia.

This patient was the sickest of any of the patients who recovered. The administration of antitoxin, which was started on the fourteenth day, was continued until a total of 420,000 units had been given by the twenty-third day. During the same time 535 cc. of immune blood was given. The temperature returned to normal by the thirty-fourth day and remained so until the fiftieth, when the

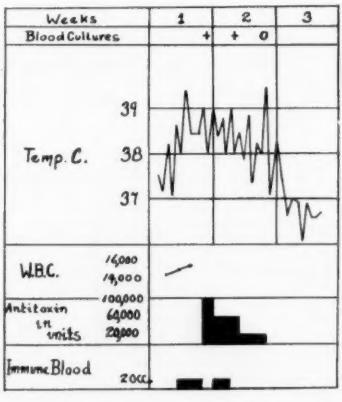

Chart 5.—Data on case 6.

patient was allowed to sit in a chair for fifteen minutes. The second episode began here with a rising temperature, which by the fifty-seventh day reached 39.6 C. (103.4 F.). The administration of antitoxin was again started, and during the next eight days an additional 320,000 units was given. The temperature quickly returned to normal. A total of 740,000 units of antitoxin and 535 cc. of immune blood was given. The patient left the hospital on the ninety-second day to convalesce at his home in southern California. Recent reports have shown a steady return to health without complications.

CASE 6 (permission of Dr. Ruby Cunningham).—A white girl aged 18 entered the hospital complaining of a furuncle of the forehead of four days' duration and a temperature of 38.1 C. (100.6 F.). It was known that she had diabetes mellitus. Physical examination revealed nothing abnormal except a large furuncle of the right side of the forehead, a swelling of the eyelids severe enough to close both eyes and an elevated temperature. Laboratory reports on the urine showed: dextrose 4 plus, and acetone, 2 plus. These conditions were quickly brought to normal with proper diet and insulin. The white blood cell count ranged between

11,700 and 24,100. Blood cultures were positive for Staph. aureus on the sixth and ninth days. Between the fourth and ninth days, a total of 100 cc. of immune blood was given. Between the time that the blood culture was reported positive on the sixth day to the thirteenth day, a total of 340,000 units of antitoxin was given. The temperature remained normal after the fifteenth day, and the patient was dismissed on the twenty-ninth day. Recovery was complete.

CASE 7.—A white youth aged 21 gave a history of sleepiness and dizziness for three weeks, which with other signs led to a diagnosis of encephalitis. During a dizzy spell he struck his right cheek against the wall. Soon after, a furuncle developed on the same cheek, attended by a rise in temperature; so he entered the hospital. Physical examination showed a discharging furuncle with surrounding redness and edema of the right cheek. The tonsils were chronically infected. There was some weakness of the left triceps muscle. Otherwise the examination gave negative results. Laboratory examination showed the urine to be normal, except for an occasional white blood cell. The examination of the blood showed that the white cell count ranged between 4,100 and 10,700. Blood cultures were positive on the fourth and seventh days for Staph. aureus. The patient's temperature ranged from 37 C. (98.6 F.) to 39 C. (102.2 F.) Between the seventh and four-

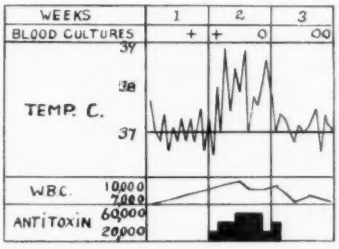

Chart 6.—Data on case 7.

teenth days 340,000 units of antitoxin was administered. The boy was dismissed from the hospital on the thirty-ninth day with a low grade fever. A recent letter reported that his strength had returned to normal.

SUMMARY

The case histories of 7 students between 18 and 23 years of age who had staphylococcic septicemia are reported. These 7 patients were the total number to have an infection of the blood stream among a total of 11,568 patients with carbuncles, furuncles and blisters during a period of thirty years. Two of the 7 patients died, or 28.6 per cent. Of the 6 patients treated with antitoxin, 3 of whom received immune blood, only 1 died, or 16.7 per cent. As to complications, of 3 who had bilateral bronchopneumonia, 1 died; of 3 who showed signs of genitourinary involvement, 1 died; and of 2 with osteomyelitis, 1 died. The doses of antitoxin varied from 340,000 to 1,080,000 units. Three of the patients who recovered received from 100 to 535 cc. of immune blood, and 2 received 1.9 cc. of toxoid during convalescence.

CONCLUSIONS

1. The treatment of staphylococcic septicemia should not be considered hopeless, since by early active treatment the mortality can be reduced.

2. Patients having active or recently healed carbuncles, furuncles or blisters, with either prolonged, mounting or septic temperatures for which no cause can be found, patients with symptoms and signs of a beginning osteomyelitis and patients with staphylococci in the blood should immediately have heroic treatment.

3. At present there is no standard as to what constitutes such treatment.

4. Experience suggests that in addition to supportive and surgical care, early treatment with large doses of antitoxin in a total dosage varying from 300,000 to 1,000,000 or more units,[9] together with some bactericidal element such as immune blood, gives encouraging results.

9. Since submitting this article, I have been administering antitoxin intravenously in daily doses of 100,000 units and decreasing the amount only as improvement in signs and symptoms justifies it.

OIL ASPIRATION (LIPOID) PNEUMONIA IN ADULTS

A CLINICOPATHOLOGIC STUDY OF FORTY-SEVEN CASES

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In recent years a condition commonly known as lipoid pneumonia but more appropriately termed oil aspiration pneumonia [1] or simply oil pneumonia [2] has been brought to the notice of the medical profession with increasing frequency. The outstanding features of the disease have been described at length by many writers, and attention has been repeatedly drawn to the danger of using oily medication for infants and, to a lesser degree, for adults. Despite this, it is apparent from the errors in clinical diagnosis detected at postmortem examination that many physicians are still not aware of the relative frequency of this condition, particularly in adults.

Laughlen [3] in 1925 reported 5 instances of oil pneumonia in human beings, 1 of whom was a man aged 37. The condition had been produced experimentally, however, at an earlier date. Guieysse-Pellissier [4] in 1920 observed that intratracheal instillation of olive oil was capable of producing a mononuclear and polymorphonuclear response in the

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1. (*a*) Ikeda, K.: Oil Aspiration Pneumonia (Lipoid Pneumonia), Am. J. Clin. Path. **5**:89 (March) 1935; (*b*) Oil Aspiration Pneumonia (Lipoid Pneumonia), Am. J. Dis. Child. **49**:985 (April) 1935. (*c*) Houck, G. M.: Pulmonary Oil Tumors; Granulomata Caused by Intratracheal Instillation of Liquid Petrolatum (Lipoid or Oil Aspiration Pneumonia), in Medical Papers Dedicated to Henry Asbury Christian, in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, 1936, pp. 463-478. (*d*) Fetterman, G. H.: Oil Aspiration Pneumonia, J. Lab. & Clin. Med. **22**:619 (March) 1937.

2. (*a*) Hayes, J. N., and Gardner, L. V.: Oil Pneumonia, Experimental and Clinical, Tr. Am. Clin. & Climat. A. **50**:192, 1934. (*b*) Ritchie, G.: Oil Pneumonia, Wisconsin M. J. **35**:286 (April) 1936.

3. Laughlen, G. F.: Studies on Pneumonia Following Naso-Pharyngeal Injections of Oil, Am. J. Path. **1**:407 (July) 1925.

4. Guieysse-Pellissier, A.: Recherches sur l'absorption de l'huile dans le poumon, Compt. rend. Soc. de biol. **83**:809, 1920.

lungs of animals. Corper and Freed [5] in 1922 demonstrated that liquid petrolatum so introduced into rabbits induced proliferative bronchopneumonia. Similar results were obtained with olive oil, while chaulmoogra oil produced a violent pulmonary inflammation. In 1927, Pinkerton [6] reported several cases of oil aspiration pneumonia in infants and found that a number of fats and oils were responsible agents in patients of this age group; at this time he also made a study of the staining reactions of the various oils in the lung. In 1928 the same author [7] published the results of a thorough experimental study of pulmonary reactions to animal, vegetable and mineral oils. Using rabbits, he demonstrated that animal oils, such as cod liver oil, milk fat and lard oil, produced fibrosis and giant cell formation in the lung together with necrosis and edema depending on the amount of free fatty acid present in the oil or liberated in the lung by hydrolysis. Vegetable oils, such as as the iodized sesame and poppyseed oils used in bronchography, and olive oil [8] produced practically no reaction. A notable exception to this was chaulmoogra oil. Liquid petrolatum induced a marked macrophagic response together with giant cell formation and some fibrosis by the end of the second or the third month. The amount of fibrosis in the experimental animals, however, was in no way comparable to that which he had observed in 2 infants in whom liquid petrolatum had entered the lungs. This work has since been widely corroborated and enlarged on by others, among them Ikeda [10] and Paterson.[9]

Ikeda [10] summarized the literature up to April 1936 and listed 106 cases; 39 of the patients were adults. In a thorough review of the literature through March 1939 we have been able to bring the total number of adult patients to 58, including 2 girls aged respectively 14 and 17 years. In 42 cases the diagnosis was either established or confirmed at autopsy.

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5. Corper, H. J., and Freed, H.: The Intratracheal Injection of Oils for Diagnostic and Therapeutic Purposes, J. A. M. A. **79**:1739 (Nov. 18) 1922.

6. Pinkerton, H.: Oils and Fats: Their Entrance into and Fate in Lungs of Infants and Children, Am. J. Dis. Child. **33**:259 (Feb.) 1927.

7. Pinkerton, H.: Reaction to Oils and Fats in the Lungs, Arch. Path. **5**:380 (March) 1928.

8. Considerable discrepancy in the results obtained with olive oil is evident in early reports. Since commercial olive oil may contain a highly variable amount of free fatty acid, it seems likely that the differences in experimental results are due for the most part to this variation and that the nonirritating character of the oil used by Pinkerton in his experiments was due to its low fatty acid content.

9. Paterson, J. L. H.: Pneumonia Following Aspiration of Oily Substances: Lipoid Cell Pneumonia, J. Path. & Bact. **46**:151 (Jan.) 1938.

10. Ikeda, K.: Lipoid Pneumonia of Adult Type (Paraffinoma of Lung), Arch. Path. **23**:470 (April) 1937.

We are reporting on a group of 47 additional adult patients, ranging in age from 20 to 82 years. Of these, 41 were chosen from about 3,500 consecutive autopsies performed at the Montefiore Hospital during the past ten years. Only those cases were considered in which the microscopic observations were characteristic and the gross pictures at least reasonably compatible with the diagnoses so far as they were described. Since macrophages filled with lipoid material may be seen in the lesions of pulmonary tuberculosis (especially tuberculous pneumonia) or in the vicinity of large infarcts, cases in which such conditions were present were selected only if the pathologic picture and the staining reactions [11] offered incontrovertible evidence of the nature of the etiologic agent and if at least one lipoid area was in a lobe other than that involved by the tuberculous or the hemorrhagic process. Finally, all cases were omitted in which only a few foam cells or oil droplets were found, since the condition in these was felt to be due in all probability to terminal aspiration.

Six additional cases in which the clinical and roentgen findings are characteristic of this disease and in which the patients are in the hospital wards at the time of writing have also been included. Some of these cases were discovered by routine roentgen examination of patients with dysphagia in the neurologic service. A seventh patient, originally in this group, died during this study, and the diagnosis was confirmed at autopsy (case 41).

We are able to present this unusually large series chiefly because the Montefiore Hospital is an institution for chronic diseases. There are in its wards many elderly persons suffering with debilitating illnesses in advanced stages, and such persons are particularly likely to have oil pneumonia. This is reflected in the fact that in our postmortem group the average age of the patients (at death) was 61.8 years as compared with 53.6 years, the average age of the patients previously reported on. Patients in the neurologic service, in whom the frequency of dysphagia makes oil aspiration pneumonia a common complication, form a younger age group. Thus, the average age of our 6 clinical patients is 35 years, and that of 5 similar "neurologic patients" in the group studied post mortem was 45.4 years.

Liquid petrolatum was by far the most important etiologic agent in the production of this condition in our series and in the cases of the 58 adults described in the literature. In the latter group this substance was definitely the etiologic agent in 47. In 9 additional cases the oil

11. Liquid petrolatum stains a pale orange with scarlet red and pink with nile blue sulfate and if uncontaminated by other fats and oils does not reduce osmic acid. On extraction from tissue it can be readily identified by its high boiling point, its failure to saponify and its negative reaction to the acrolein test.

was not identified and no definite history was available, and it is therefore not possible to determine in how many of these the condition may also have been due to liquid petrolatum. Among our cases there was 1 (case 19) in which much of the alveolar exudate was necrotic and contained scattered macrophages together with oil which reduced osmic acid but was not further identified. The patient, however, had been receiving liquid petrolatum by mouth, and there was some evidence of this oil in the lung as well. In 2 cases in which extensive liquid petrolatum pneumonia with superimposed infectious bronchopneumonia was present, a few of the alveoli contained similar necrotic exudate, suggesting the presence of an animal fat or oil probably originating in the food. In 2 additional cases, in which liquid petrolatum had been used together with cod liver oil and glycerin respectively, there was no discernible evidence to indicate that the latter two substances had played any part in the development of the lesions. Most of the patients in this series were known to have been habitual users of liquid petrolatum in relatively large quantities. The oil had been taken by mouth, intranasally (as drops, sprays, packs or douches) or intratracheally (usually as a lubricant in cases of tracheotomy); the frequency of the various routes is indicated in table 1. It will be noted that the incidence of use of the oral route among our patients is comparatively high. This is easily explained by the fact that oil is commonly used as an intestinal lubricant by chronic invalids. This may well have been the method of administration employed by our 6 patients for whom the route is listed as unknown, since most of these gave histories of having used "laxatives" habitually prior to admission to the hospital. The 1 patient by whom the intratracheal route was used employed a petroleum jelly to lubricate an operative stoma and a tracheotomy tube.

The fats and oils of animal origin which play such a significant part in the production of this condition in infants and young children are of much less importance in the case of adults. Cream was the etiologic agent in the case reported by Thomas and Jewett,[12] and cod liver oil was the causative factor in another.[13] Vegetable oils, particularly the iodized poppyseed oil and iodized sesame oil used in bronchography, are rare offenders, as they are chemically nonirritating; in addition, they are used in relatively small quantities and are frequently absorbed or expectorated rapidly. That such elimination can occur even in the presence of pulmonary lesions due to liquid petrolatum was demonstrated in the cases of 2 of our patients for whom bronchographic

12. Thomas, W. S., and Jewett, C. H.: Pneumonia Following Aspiration of Fats from the Esophagus Dilated as a Result of Cardiospasm, Clifton M. Bull. **12**:130 (Dec.) 1926.

13. Young, A. M.; Applebaum, H. S., and Wasserman, P. B.: Lipoid Pneumonia, J. A. M. A. **112**:2406 (June 10) 1939.

examinations were made. Bezançon, Delarue and Valet-Bellot [14] performed autopsies on 3 patients who died two days, twelve days and six years respectively after the intratracheal administration of this oil, and noted slight phagocytosis of the oil in the interstitial tissue but

TABLE 1.—*Routes of Administration of Oil to Adult Patients*

Author	Cases Reported	Autopsy Performed	Route of Administration: Oral	Nasal	Oral and Nasal	Intratracheal	Unknown and Unreported
Laughlen [3]	1	1	1	..	..	..	..
Thomas and Jewett [12]	1	1	1	..	..	..	..
Fischer-Wasels, B.: Tödliche Lungenschrumpfung durch Gebrauch von Mentholöl, Frankfurt. Ztschr. f. Path. **44**: 412, 1933	1	1	..	1	..	..	..
Bodmer, H., and Kallós, P.: Ueber schwere Lungenschädigung (Lungenzirrhose) in folge Aspiration von Paraffinöl bei therapeutisches Anwendung, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **136**: 40 (April) 1933	1	0	..	1	..	..	..
Meursing, F.: Pneumonoliposis, Nederl. tijdschr. v. geneesk. **77**: 3878 (Aug.) 1933	2	2	..	..	..	..	2
Ellinger, E.: Paraffinölschädigung der Lunge, Fortschr. a. d. Geb. d. Röntgenstrahlen **49**: 397 (April) 1934	3	1	..	..	..	3	..
Hayes and Gardner [2a]	2	2	..	2	..	..	..
Grayzel, D. M., and DuMortier, J. J.: Pneumonia in Children Following Aspiration of Oil and Fat, Yale J. Biol. & Med. **6**: 599 (July) 1934	1	1	1	..	..	..	..
Graef, I.: Pulmonary Changes Due to Aspiration of Lipids and Mineral Oil, Am. J. Path. **11**: 862 (Sept.) 1935	3	3	2	..	..	..	1
Ball, F. E.: Petroleum Oil Pneumonia in an Adult, Illinois M. J. **69**: 62 (Jan.) 1936	1	1	1	..	..	..	..
Davis, K. S.: Mineral Oil in the Lung, Radiology **26**: 131 (Feb.) 1936 *	3	1	..	2	..	1	..
Tebertkoff, I. G., and Ornstein, G. G.: Bronchopulmonary Disease Attributed to the Use of Intranasal Instillation of Oily Substances, Quart. Bull., Sea View Hosp. **1**: 139 (Jan.) 1936	9	0	..	9	..	..	..
Ritchie [2b]	10	10	6	..	1	..	3
Ikeda [10]	5	5	1	3	..	..	1
Fetterman [14]	2	2	2	..	..	..	..
Paterson [9]	6	6	..	..	..	..	6
Ellinger [24]	3	1	..	..	..	3	..
Walsh and Cannon [21]	3	3	..	2	..	..	1
†Young, Applebaum and Wasserman [13]	1	1	1	..	..	..	..
Literature (total)	58	42	16	20	1	7	14
This series (postmortem group)	41	41	29	3	2	1	6
This series (clinical group)	6	0	4	..	2	..	..
Total	105	83	49	23	5	8	20

* One of these cases was also reported by Houck, G. M.: Intratracheal Instillation of Liquid Petrolatum: Pulmonary Injury Therefrom, California & West. Med. **49**: 187 (Sept.) 1938. Footnote 1c.

† This case was previously cited by Kline, B. S.: Pathology of Chronic Non-Tuberculous Inflammations of the Lung, Am. Rev. Tuberc. **38**: 663 (Dec.) 1938.

little other histologic reaction. It appears, however, that iodized poppy-seed oil can produce reactions under exceptional circumstances. Rabino-

14. Bezançon, F.; Delarue, J., and Valet-Bellot, M.: Le sort du lipiodol dans le parenchyme pulmonaire chez l'homme, Ann. d'anat. path. **12**:229 (March) 1935.

vitch and Lederer [15] mentioned a case in which the changes seen at necropsy were those associated with lipoid pneumonia. Wright [16] reported another in which a granuloma was produced by oil trapped by a bronchial neoplasm. In the latter case the appearance resembled the normal walling off of a foreign body that cannot be removed rather than a reaction attributable to the chemical nature of the oil. Ordinarily vegetable oils induce little or no macrophagic response.

It has been repeatedly demonstrated that oil introduced into the pharynx is capable of entering the bronchial tree without exciting reflex inhibition. Quinn and Meyer [17] instilled iodized poppyseed oil into the nose during sleep and found that it quickly entered the trachea and bronchi. Pirie [18] mentioned a comparable experiment. Experimental work on animals [19] also seems to demonstrate the fact that liquid petrolatum, being bland and nonirritating to the pharyngeal mucosa, does not stimulate reflex closure of the glottis and fails to elicit a cough reflex. In addition, it hinders ciliary activity by mechanically slowing up or stopping the stream of mucus normally set up by the beat of the cilia.[20] Aspiration of the oil is thus favored by the ease with which it can enter the respiratory passages and by interference with the protective mechanisms designed to expel foreign matter from them.

These considerations are important in the genesis of oil pneumonia in infants and in adults who either habitually use oil intranasally or into whose nostrils oil is introduced during somnolent or irrational states. Thus, in Walsh and Cannon's [21] cases 2 of the patients were apparently healthy men who had been using oil intranasally and died by suicide, and a third was a young comatose girl into whose conjunctival sacs oil was repeatedly introduced. In adults who take oil orally, pathologic processes which interfere with normal cough, palatal or swallowing reflexes become important predisposing factors. The condition is therefore frequently encountered in debilitated, recumbent and aged persons, in persons with dysphagia of nervous origin and in patients in whom

15. Rabinovitch, J., and Lederer, M.: Lipoid Pneumonia, Arch. Path. **17**:160 (Feb.) 1934.

16. Wright, R. D.: Reaction of Pulmonary Tissue to Lipiodol, Am. J. Path. **11**:497 (May) 1935.

17. Quinn, L. H., and Meyer, O. O.: Relationship of Sinusitis and Bronchiectasis, Arch. Otolaryng. **10**:152 (Aug.) 1929.

18. Pirie, A. H., in discussion on Pierson, J. W.: Some Unusual Pneumonias Associated with the Aspiration of Fats and Oils, Am. J. Roentgenol. **27**:572 (April) 1932.

19. Ikeda.[1a] Laughlen.[3]

20. Proetz, A. W.: Effects of Certain Drugs on Living Nasal Ciliated Epithelium, Ann. Otol., Rhin. & Laryng. **43**:450 (June) 1934.

21. Walsh, T. E., and Cannon, P. R.: Problem of Intranasal Medication, Ann. Otol., Rhin. & Laryng. **47**:579 (Sept.) 1938.

neoplastic or other destructive processes involve the mouth and throat. The nonirritating character of the oil makes its aspiration by such persons particularly likely, although occasionally other substances and food particles may be aspirated as well. Finally, tracheotomy may predispose to the condition if the oil (or other petroleum product) is used for lubrication of the airway.

Once aspirated, the disposition of the oil in the lung appears to depend almost exclusively on mechanical factors. In a study of pulmonary inspiration and aspiration of fluid in rabbits and dogs, Corper,[22] using india ink, found that the substance was patchy in its localization and showed a tendency toward immediate aspiration into the alveoli. It seemed probable to him, on the basis of his experiments that the disposition of the fluid is dependent entirely on gravity and inspiratory suction. The importance of gravity as a prime factor in determining the position of the lesions is further borne out by the work of others. Walsh and Cannon [21] injected oil into the nasal passages of rabbits held in the sitting and in the vertical position and found in each instance localization of the oil in the lowermost portions of the lungs. A study of our own postmortem series confirms these conclusions. Thus, the lower lobe of the right lung was involved in 34 instances, the lower lobe of the left in 29, the middle lobe of the right in 25, the upper lobe of the right in 16 and the upper lobe of the left in 13. It is evident from these figures that the dependent portions of the lungs are predominantly involved and that the right lung is more often involved than the left. In addition, the lower portions of the individual lobes are most often affected. In only 2 instances were the upper lobes alone involved. In 11 patients involvement of the upper lobes was part of an extensive process, although in 1 of these the process began in the upper lobe of the right lung, as was proved by roentgen examination (case 27).

PATHOLOGIC PICTURE

The response of the lung to the aspiration of liquid petrolatum is twofold. A macrophagic reaction characterizes the early stages and occurs very promptly. This is followed and gradually replaced by fibrous proliferation of the interstitial tissue, which develops much more slowly and appears to be in large measure a foreign body reaction. As the lesion increases in size, the fibrosis becomes more and more prominent, and at the same time the macrophages tend to disappear.

The initial response is characteristic. Phagocytes accumulate in large numbers in the alveolar spaces, where they quickly take up the oil which is present there in a rather fine state of subdivision. The numerous droplets of varying size give the cells, if small, a foamy appearance or,

22. Corper, H. J.: Pulmonary Aspiration of Particulate Matter, Normally and During Anaesthesia, J. A. M. A. **78**:1858 (June 17) 1922.

TABLE 2.—*Group Studied Post Mortem*

Patient	Age at Death, Sex	Major Diagnosis	Time in Hospital	Etiologic Agent: Oil	Etiologic Agent: Time Taken (Minimal)	Etiologic Agent: Route	Predisposing Factors	Pulmonary Symptoms	Pulmonary Signs	Roentgen Examination of Chest	Autopsy: Involvement	Autopsy: Gross Appearance	Autopsy: Microscopic Appearance†
1 M. C.	45 M	Multiple sclerosis	14 yr.	Liquid petrolatum	5 yr.	Oral	Dysphagia	3 episodes of bronchopneumonia; chronic cough	Dulness; rales and bronchial breath sounds in R.L.L., and L.L.L.	"Positive"	All lobes	Massive, firm yellow-brown consolidation	Oil pneumonia in all stages; oil in hilar node
2 L. L.	66 F	Carcinoma of rectum	2 yr.	Liquid petrolatum	2 yr.	Oral	Recumbency	None	None	.....	L.L.L.* L.U.L.	Firm, nodular small gray areas; white fluid exudate	Moderately advanced to advanced oil pneumonia
3 B. S.	64 F	Carcinoma of stomach	4 mo.	Liquid petrolatum	3 mo.	Oral	Recumbency	None	Dulness and diminished breath sounds at both bases; no other signs	.....	Base of R.U.L.	Discrete, firm gray consolidated areas	Moderately advanced to advanced oil pneumonia
4 N. B.	57 M	Diabetes; residual hemiplegia	4 yr.	Liquid petrolatum	4 yr.	Oral	Paralysis of hypoglossal nerve	None	None	.....	All lobes	Scattered, small firm gray areas; white fluid exudate	Early oil pneumonia; bronchopneumonia; congestion
5 J. G.	60 M	Carcinoma of tongue	10 mo.	Liquid petrolatum	2 mo.	Oral	Dysphagia; oral pathologic condition	None	None	No abnormality †	All lobes	Firm, yellow areas of consolidation	Early to moderately advanced oil pneumonia
6 E. S.	65 F	Arteriosclerosis; coronary occlusion	1 yr.	Liquid petrolatum	7 mo.	Oral	Weakness	None	Dulness, rales and bronchial breath sounds in R.L.L., R.M.L.	No abnormality †	All lobes	Upper lobes fibrotic and gray; lower lobes mottled, yellow-gray consolidation; purulent foci	Early to moderately advanced oil pneumonia; bronchitis; bronchiolitis
7 N. C.	79 M	Carcinoma of cheek	2 yr.	Liquid petrolatum	3 mo.	Oral	Dysphagia; oral pathologic condition	None	None	"Positive"	R.L.L.	Large, gray, consolidated areas; yellow fluid exudate	Early to advanced oil pneumonia; bronchopneumonia
8 M. S.	75 M	Carcinoma of cecum	4 mo.	Liquid petrolatum	2 wk.	Oral	Recumbency	None	None	No abnormality †	R.U.L. R.M.L. R.L.L. L.L.L.	Small, firm, nodular pinkish to dirty gray areas with surrounding consolidation in lower lobes	Early to advanced oil pneumonia; few small areas of necrotic exudate (food fat ?); bronchopneumonia
9 J. L.	55 M	Dermatitis vegetans	1 yr.	Liquid petrolatum	7 mo.	Oral	Recumbency	None	None	.....	R.M.L.	Firm, discrete, pea-sized gray nodules	Advanced oil pneumonia (paraffinoma)

10 Y. S.	66 F	Tuberculosis of spine	4 yr.	Liquid petrolatum	4 yr.	Oral	Recumbency	None	Bilateral basal rales	No abnormality †	R.L.L. L.L.L.	Firm, yellow-gray areas containing purulent foci; surrounding diffuse red-gray consolidation	Early to advanced oil pneumonia; bronchiolitis; patchy bronchopneumonia
11 M. M.	82 M	Carcinoma of rectum	3 wk.	Liquid petrolatum	3 wk.	Oral	Recumbency	None	None	.....	R.U.L. R.M.L. R.L.L. L.L.L.	Firm, gray, mottled areas of consolidation	Early to moderately advanced oil pneumonia; bronchopneumonia
12 M. H.	72 M	Carcinoma of larynx	2 mo.	Liquid petrolatum	2 mo.	Tracheotomy tube	Tracheotomy	None	None	No abnormality	R.L.L. L.L.L.	Firm consolidation; congestion	Early oil pneumonia
13 M. S.	67 M	Arteriosclerosis; coronary occlusion	2 yr.	Liquid petrolatum	6 mo.	Oral	Recumbency	None	Dulness; rales, friction rub at right base	"Positive"	R.L.L. L.L.L.	Firm, yellow, patchy consolidation; thrombus in left pulmonary artery	Moderately advanced oil pneumonia; bronchopneumonia
14 M. B.	53 M	Hypertension; cerebral thrombosis	1 yr.	Liquid petrolatum; glycerin	9 mo. 1 yr.	Oral	Weakness	Low grade fever	Dulness; bronchial breathing; rales	"Positive"	R.M.L. R.L.L. L.U.L.	Firm, dirty gray-yellow areas of consolidation	Early to moderately advanced oil pneumonia; patchy bronchopneumonia
15 B. A.	54 M	Amyotrophic lateral sclerosis	10 mo.	Liquid petrolatum	4 mo.; 1 mo.	Oral; nasal	Dysphagia	None	Rales; diminished breathing at both bases	.....	R.L.L. L.L.L. (bases)	Irregular, brownish yellow areas of consolidation	Early oil pneumonia; bronchopneumonia
16 B. F.	37 F	Carcinoma of larynx	1 mo.	Liquid petrolatum	3 wk.	Nasal	Recumbency	None	None	.....	R.L.L. (base)	Pea-sized, firm yellow areas	Early oil pneumonia
17 D. G.	68 M	Nonunited fracture of femur	6 yr.	Liquid petrolatum	5 yr.	Oral	Recumbency	None	Increased fremitus; rales; diminished breath sounds	"Positive"	R.M.L. R.L.L. L.L.L.	Rt.—Granular, gray white, firm, tissue. Empyema. Lt.—Dirty gray consolidation	On right, advanced oil pneumonia (paraffinoma); on left, moderately advanced oil pneumonia; bronchopneumonia
18 A. B.	79 F	Carcinoma of rectum	1½ yr.	Liquid petrolatum	15 mo.	Oral	Weakness	Low grade fever	None	"Positive"	R.L.L. L.L.L.	Nodular, firm gray areas of consolidation	Early to moderately advanced oil pneumonia
19 P. L.	74 M	Carcinoma of stomach	2 mo.	Liquid petrolatum	1 mo.	Oral?	Dysphagia; vomiting; marked recumbency	None	None	No abnormality †	L.U.L. L.L.L. (bases)	Firm, dull, gray to red-gray areas of consolidation; oil exuded	Areas of necrotic exudate with partially disintegrated lipophages; some fibrosis; few areas contain oil-filled macrophages, no necrosis; most of oil reduced osmic acid; bronchopneumonia in R.U.L.

TABLE 2.—*Group Studied Post Mortem*—Continued

Patient	Age at Death, Sex	Major Diagnosis	Time in Hospital	Etiologic Agent: Oil	Etiologic Agent: Time Taken (Minimal)	Etiologic Agent: Route	Predisposing Factors	Pulmonary Symptoms	Pulmonary Signs	Roentgen Examination of Chest	Autopsy: Involvement	Autopsy: Gross Appearance	Autopsy: Microscopic Appearance†
20 M. G.	39 F	Carcinoma of breast	5 mo.	Liquid petrolatum	5 mo.	Oral	Recumbency	Low grade fever	Rales; diminished breathing at right base	No abnormality	R.U.L. R.L.L. (bases)	Firm, bright yellow areas of consolidation	Early oil pneumonia (tumor in lymphatics)
21 A. B.	56 M	Rheumatoid arthritis; rheumatic heart disease	5 yr.	Liquid petrolatum	5 yr.	Oral	Recumbency	Chronic cough	None	"Positive"	R.M.L.	Firm gray nodules; thick fluid exudate; fibrinous pleurisy	Moderately advanced to advanced oil pneumonia
22 H. H.	68 M	Carcinoma of palate	6 mo.	Liquid petrolatum	Months	Nasal	Oral pathologic condition	Chronic cough	Dulness; bronchial breathing	"Positive"	R.M.L. L.L.L.	On right, firm gray consolidation; oil exuded; on left, pea-sized firm granular areas	Moderately advanced to advanced oil pneumonia (paraffinoma); congestion
23 L. G.	69 F	Hypertension; coronary occlusion	4½ yr.	Liquid petrolatum	1½ yr.	Oral	Weakness	Chronic cough	Rales at both bases	"Positive"	All (only bases of upper lobes)	Extensive, firm, gray areas of consolidation; purulent exudate in bronchi	Early to moderately advanced oil pneumonia; marked congestion
24 E. O.	28 F	Postencephalitic parkinsonism	8 yr.	Liquid petrolatum	10 mo.	Oral	Weakness	None	Dulness; rales	.....	R.M.L. R.L.L. L.L.L. L.U.L.	Granular, gray-yellow diffuse areas of consolidation with purulent foci	Early to moderately advanced oil pneumonia; oil in hilar nodes
25 J. R.	59 M	Carcinoma of colon	1 yr.	Liquid petrolatum	11 mo.	Oral	Weakness	Low grade fever	Basal rales on right	"Positive"	R.L.L. L.L.L.	Firm, gray-white walnut-sized nodules; tuberculosis in upper lobes	Moderately advanced oil pneumonia; bronchiolitis; patchy bronchopneumonia
26 A. H.	60 M	Hypertensive heart disease	11 mo.	Liquid petrolatum	Many years; 15 mo.	Nasal; Oral	None	Chronic cough; low grade fever	Loud bronchial breathing at base of left lung	"Positive"	R.M.L. R.L.L. L.L.L.	Firm consolidation and fibrosis; oil exuded; obliterated right pleural space; moderate bronchiectasis of lower lobes; lobar pneumonia in L.U.L.	Moderately advanced to advanced oil pneumonia; patchy bronchopneumonia; oil in hilar nodes
27 L. K.	42 F	Scleroderma	29 yr.	Liquid petrolatum; cod liver oil	10 yr.; 2 yr.	Oral	Difficulty in opening mouth	Chronic cough; pain in chest; low grade fever; several episodes of bronchopneumonia	Dulness; bronchial breathing; rales	"Positive"	R.U.L. R.M.L. R.L.L.	Firm, gray consolidation with fibrous strands; purulent foci, pleural adhesions	Advanced oil pneumonia (paraffinoma)
28 D. W.	70 F	Hypertension; hemiplegia	3 yr.	Liquid petrolatum	20 mo.	Oral	Recumbency	Chronic cough	Rales; bronchial breathing at R.L.L.	"Positive"	R.U.L. R.L.L. L.L.L.	Firm, granular gray consolidation; purulent foci; slight bronchiectasis; healed apical tuberculosis	Early to moderately advanced oil pneumonia; bronchitis with slight bronchopneumonia

29 J. R.	55 F	Arteriosclerosis; hypertension	1½ yr.	Liquid petrolatum	4 mo.	Oral	Weakness	Chronic cough; low grade fever; several episodes of bronchopneumonia	Dulness; rales; increased fremitus; bronchial breathing	No abnormality †	All (bases of upper lobes)	Yellow to yellow-pink granular consolidation; purulent foci	Moderately advanced to advanced oil pneumonia; few small areas of necrotic exudate (food fat?); bronchiolitis; bronchopneumonia
30 W. L.	63 M	Carcinoma of lung	1½ yr.	Liquid petrolatum	7 mo.	Oral	Weakness	Chronic cough	Dulness; diminished breath sounds	"Positive"	L.U.L. (lower outer part)	Firm, gray, tumor-like consolidation; tumor in R.L.L.	Moderately advanced to advanced oil pneumonia
31 A. G.	53 M	Chronic anterior poliomyelitis	17 yr.	Liquid petrolatum	17 yr.	Oral	Recumbency	Chronic pain in chest	Dulness; rales; diminished breathing	.....	R.M.L. R.L.L. (hilar) L.L.L.	On right, firm consolidation with purulent foci; on left; patchy consolidation	Early to moderately advanced oil pneumonia; advanced (paraffinoma) in a few small areas; marked congestion
32 A. G. *	63 F	Arteriosclerotic heart disease	1 wk.	Liquid petrolatum	1 wk.	Oral	Recumbency	None	None	.....	R.L.L. L.L.L.	Areas of pale consolidation	Early to moderately advanced oil pneumonia; bronchopneumonia (early)
33 N. W.	72 M	Arteriosclerotic heart disease	1 mo.	.....	.....	.....	.....	.....	Dulness; diminished breath sounds	"Positive"	R.M.L. R.L.L. L.L.L.	Firm, gray fibrous tissue; bronchiectasis	All stages of oil pneumonia; advanced stage (paraffinoma) most prominent
34 I. H.	62 M	Arteriosclerosis; subarachnoid hemorrhage	2 days	.....	.....	.....	.....	.....	.....	.....	R.U.L. R.M.L. R.L.L. (bases)	Firm, pale yellow-gray masses	Early to moderately advanced oil pneumonia; bronchopneumonia
35 M. M.	76 M	Carcinoma of maxillary sinus	18 days	.....	.....	.....	Oral pathologic condition	None	None	"Positive"	R.M.L. R.L.L. (adjoining portions near hilus)	Firm, pale gray tissue, well circumscribed; fibrosis in R.L.L.; obliterated pleural space	Moderately advanced to advanced oil pneumonia (paraffinoma); bronchopneumonia
36 R. K.	79 F	Hypertension; hemiplegia	3 wk.	Liquid petrolatum	.....	.....	Recumbency	Chronic cough; persistent pain in chest	Dulness; rales; increased fremitus	"Positive"	R.L.L.	Firm, gray mass; oil exuded; bronchiectatic abscess in L.U.L.	Advanced oil pneumonia (paraffinoma)
37 C. S.	81 M	Carcinoma of floor of mouth	3 days	.....	.....	.....	Oral pathologic condition	.....	Rales; bronchial breathing	.....	R.M.L. R.L.L. L.U.L. L.L.L. (adjoining portions)	Gray-white and yellow-white firm consolidation; yellow, frothy fluid exudate	Moderately advanced to advanced oil pneumonia; bronchopneumonia in R.L.L.

TABLE 2.—*Group Studied Post Mortem*—Continued

Patient	Age at Death, Sex	Major Diagnosis	Time in Hospital	Etiologic Agent: Oil	Etiologic Agent: Time Taken (Minimal)	Etiologic Agent: Route	Predisposing Factors	Pulmonary Symptoms	Pulmonary Signs	Roentgen Examination of Chest	Autopsy: Involvement	Autopsy: Gross Appearance	Autopsy: Microscopic Appearance†
38 F. L.	59 M	Carcinoma of esophagus	4 mo.	.....	.....	.....	Dysphagia	Chronic cough; low grade fever	Rales; bronchial breathing	"Positive"	R.M.L. R.L.L. R.U.L. (base)	R.U.L. showed nodular areas of pale consolidation; others, diffuse pink-gray consolidation	Early to moderately advanced oil pneumonia; bronchopneumonia
39 S. C.	58 M	Carcinoma of stomach	6 mo.	Liquid petrolatum	.....	Oral	Dysphagia	None	Rales	No abnormality †	L.L.L. R.L.L.?	Granular, dirty pink-gray consolidation of L.L.L.; empyema on right; lower lobe small and fleshy	Moderately advanced oil pneumonia; bronchopneumonia
40 S. B.	44 M	Tumor of brain	5 mo.	Liquid petrolatum	.....	Oral	Dysphagia	Chronic cough	Rales	.....	All	Firm gray to white areas of consolidation in nodular groups	Moderately advanced to advanced oil pneumonia; bronchopneumonia
41 S. M.	56 M	Degenerative olivopontocerebellar disease	3 yr.	Liquid petrolatum	2½ yr.	Oral	Dysphagia	Repeated (3) episodes of bronchopneumonia	Dulness; rales; increased fremitus	"Positive"	R.U.L. R.M.L. R.L.L. L.L.L.	Firm gray to pink-gray consolidation; fluid containing oil exuded on compression; hilar nodes enlarged	Moderately advanced to advanced oil pneumonia (paraffinoma); bronchopneumonia

* In this table the following abbreviations are used: L.U.L., upper lobe of left lung; R.U.L., upper lobe of right lung; L.L.L., lower lobe of left lung; R.L.L., lower lobe of right lung, and R.M.L., middle lobe of right lung.

† Roentgen examination on or soon after admission; inadequate or no follow-up.

Key to description of microscopic findings:

Early.—Numerous lipophages; little or no septal proliferative reaction; varying grades of edema and congestion.

Moderately Advanced.—Lipophages numerous or diminishing; moderately advanced proliferative reaction, frequently with many cells; giant cells in varying numbers; frequent alveolar distortion and epithelization.

Advanced.—Lipophages few or absent; dense fibrosis with moderate or slight cellularity. Paraffinoma: Dense fibrosis with entrapped oil-filled spaces replacing normal parenchyma.

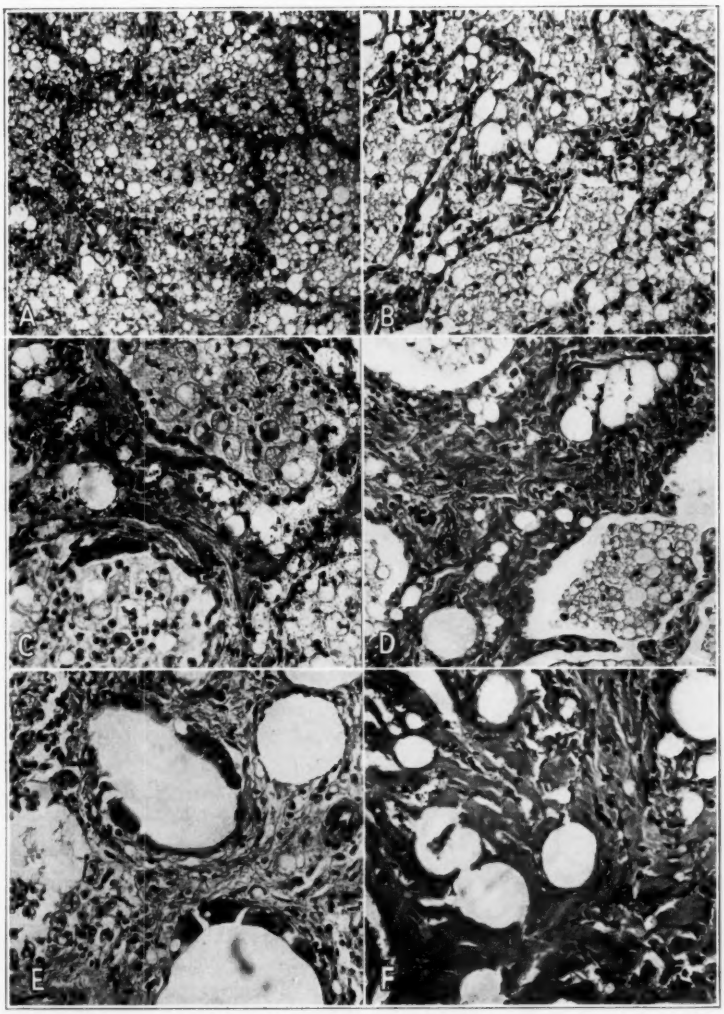

Fig. 1.—Stages in the progress of the pulmonary lesion caused by aspirated liquid petrolatum (× 139). *A*, early process. The alveoli are crowded with oil-filled macrophages. There is septal congestion but no fibrosis. *B*, extensive infiltration of the septums and lymphatics with macrophages; in many of these the oil globules have coalesced to form one large droplet. *C*, increasing septal fibrosis with entrapping of oil. Note the epithelization of the alveoli. *D*, later stage. *E*, oil-filled spaces with crescent giant cells at the periphery. Note the oil droplets in the cells. *F*, paraffinoma.

if large, a resemblance to ordinary fat cells. These are so-called lipoid cells, or lipophages. The intracellular droplets, seen by ordinary staining methods as vacuoles, are practically always well defined; the cell membrane is sharply outlined, and the cell nucleus is frequently distorted and displaced peripherally. Extracellular oil is usually present, becoming more prominent in later stages as the macrophages disintegrate. The alveolar septums may show considerable edema and some cellular infiltration if irritating medicaments have been aspirated with the oil (as when nasal sprays have been used), if organic oils or fats of animal origin have been aspirated as well or if there is associated infection. In the presence of bronchopneumonia, congestion and polymorphonuclear infiltration are prominent features.

Grossly, at this stage the involved portions of the lung are gray, gray-yellow or bright yellow, are often mottled and are moderately firm, with a spongy texture. They protrude slightly above the level of the surrounding parenchyma, and in the absence of secondary infection are usually sharply demarcated; a small amount of milky fluid may often be expressed from the surface. Unfortunately bronchopneumonia, bronchitis, pulmonary edema and chronic passive congestion are frequently present, and the entire area often has an appearance so muddy and congested that correct diagnosis is practically impossible without microscopic examination. The lesions may vary in size and distribution from pea-sized or smaller patches in one or more lobes to massive consolidation of both lungs, depending on the amount of oil aspirated and the frequency of aspiration.

As the secondary, or proliferative, reaction develops, the lesions gradually grow firmer and tend to become gray-white. Such advanced lesions may have the appearance of tumor tissue, for which they are not infrequently mistaken, and vary in size from small nodules, usually multiple, to large, firm masses involving almost an entire lobe or portions of two adjoining lobes. Oil may be readily scraped from the cut surface, and if bronchitis or bronchiolitis is present there may be a purulent exudate as well.

Microscopically, the proliferative reaction does not differ essentially from that associated with chronic interstitial pneumonitis due to other causes. In the later stages, in fact, when the lipophages are no longer seen, it is only by the finding of the oil entrapped within the dense fibrous tissue (and demonstrable by special staining or extraction), together with the presence of earlier stages of the same process in surrounding areas, that the cause can be determined. The fibrosis is at first slight; the septums are invaded by fibroblasts, plasma cells, lymphocytes and histiocytes. Oil-laden phagocytes are noted in the septums and the lymphatics very early, being sometimes so numerous that it is almost impossible to distinguish between the septum and the alveolar space.

Free oil, believed to come from disintegrated macrophages, is also seen. Part of this oil may eventually be carried to the regional lymph nodes, where it can be demonstrated, and oil has also been reported as occurring in other organs of the body, notably the spleen. Lipophages and free oil may also be seen in the small bronchioles which frequently are dilated and the seat of purulent infection.

With the advancing fibrosis the alveoli become distorted and the appearance of the lesion becomes less and less specific. Giant cells of the foreign body type, accumulations of lymphocytes and epithelization of the walls of the alveolar spaces [23] are often seen and indeed may appear much earlier. Tubercle-like structures are occasionally present. Accumulations of oil may give the appearance of small islands of adipose tissue, and crescent-shaped giant cells, often containing oil droplets, may be seen at the periphery of oil-filled alveolar remnants. With the increasing fibrosis the cellularity diminishes, and there finally remains only a mass of hyalinized fibrous tissue with entrapped oil, a true paraffinoma. Occasionally small deposits of calcium are seen.

Although the entire process in any given case may be in the same or almost the same stage of development, this appears to be the exception rather than the rule. Since oil has usually been administered over a period of years and has been aspirated in small quantities at more or less frequent intervals, the pathologic picture is that of a group of lesions rather than of a single one. Not only may lesions in various portions of the lung differ markedly if the oil that produced them was aspirated on separate occasions, but with equal frequency well defined and widely different stages are seen in contiguous microscopic fields. In several of our cases, in fact, the probable pathogenesis of the condition could be reconstructed from the changes observed in a single section.

CLINICAL CONSIDERATIONS

No specific symptoms or signs are characteristic of oil pneumonia. In many instances the disease is entirely asymptomatic, attention being drawn to the diagnosis by puzzling conditions in the chest observed on physical or roentgen examination. Much more frequently the condition remains entirely unsuspected during life and is discovered at autopsy.

23. The presence of low or high cuboidal cells lining the alveolar spaces (so-called epithelization) is usually a prominent feature but is by no means specific. It is seen in many other chronic pulmonary conditions, and its origin remains in doubt. Some authors feel that it represents true epithelization of the alveoli with cells originating in the terminal bronchioles, a view subscribed to by Ikeda (Oil Aspiration Pneumonia [Lipoid Pneumonia], Am. J. Dis. Child. **49**:985 [April] 1935; Lipoid Pneumonia of Adult Type [Paraffinoma of Lung], Arch. Path. **23**: 470 [April] 1937).

TABLE 3.—*Group Studied Clinically*

No.	Age, Sex	Major Diagnosis	Time in Hospital	Etiologic Agent: Oil	Etiologic Agent: Time Taken	Etiologic Agent: Route	Predisposing Factors	Pulmonary Symptoms	Pulmonary Signs	Roentgen Appearance
1 A. W.	20 M	Multiple sclerosis	2½ yr.	Liquid petrolatum	2 yr.	Oral	Dysphagia	Severe febrile episode of 2 months' duration (8/11/28 to 10/15/38)	Dulness; bilateral posterior rales	1/19/37 Few scattered, linear infiltrations in both lower lung fields 9/12/38 Small areas of consolidation scattered uniformly in all lobes 11/21/38 Infiltrations throughout right lung except apical portion of upper lobe of right lung; infiltrations in lower lobe of left lung 3/30/39 Persistent consolidations showing distinct fibrous character
2 J. W.	37 M	Postencephalitic parkinsonism	1½ yr.	Liquid petrolatum	1½ yr.	Oral	Dysphagia	Two episodes of low grade fever lasting for a few days	Dulness; rales at both bases posteriorly; mineral oil identified in sputum	10/21/37 Prominent lung markings in mesial part of right lower lung field 10/15/38 Partial consolidation of lower lobe of left lung and in right lung close to the cardiac shadow and extending to the diaphragm; irregular "steel wool mottling," indicating extensive fibrosis 3/30/39 No change
3 L. J.	43 M	Posttraumatic epilepsy	1½ yr.	Liquid petrolatum	Many years; 1 year	Nasal; oral	None	Two episodes of mild cough and pain in right anterior part of chest	Dulness; rales at both bases posteriorly (more on right); mineral oil identified in sputum	11/24/37 No abnormality in lungs 9/21/38 Partial consolidation in right lower lung field, in cardiohepatic angle; infiltrations in mesial portion of lower lobe of left lung 3/30/39 No change in infiltration
4 E. F.	37 F	Congenital double athetosis	4 mo.	Liquid petrolatum	Many years	Oral	Dysphagia	None	None	1/10/39 Consolidation in right lower lung field, in cardiohepatic angle; smaller consolidation in mesial portion of lower lobe of left lung
5 A. K.	41 M	Amyotrophic lateral sclerosis	2½ yr.	Liquid petrolatum	2 yr.; 2 yr.	Oral; nasal	Dysphagia	None	None	2/20/39 Consolidation in mesial part of lower lobe of left lung and in mesial portion of the right lower lobe extending to diaphragm 3/30/39 No change
6 I. S.	23 M	Multiple sclerosis	3 yr.	Liquid petrolatum	2½ yr.	Oral	Dysphagia	None	None	11/22/38 Extensive consolidation in the mesial portion of right lower lung field extending to diaphragm; consolidation in mesial portion of lower lobe of left lung 2/30/39 No change

Symptoms were present in about half of our patients, although their significance was often overlooked. Cough occurred in 13, being usually chronic, mild and occasionally moderately productive. Blood-streaked sputum, which has been reported by others, occurred only once in our series, but in this instance it was probably due to pulmonary infarction. Pain in the chest was infrequent and usually not severe. Intermittent fever, with a temperature often rising to 101 F. daily and continuing for several weeks to months, was observed in 7 of our patients; it was apparently present only when superimposed pulmonary infection was present. The clinical course in 6 instances was characterized by repeated bouts of bronchopneumonia, such as have been described in the literature. These episodes are accompanied by cough, high fever and prostration and last a few days to several weeks; any one may be terminal.

The physical findings are those associated with any chronic pneumonitis. Dulness, harsh breath sounds, bronchovesicular or bronchial breathing and rales may be present, often at the bases of one or both lungs posteriorly. With secondary bronchopneumonia the parenchyma is more widely involved and signs of pleural effusion are occasionally found. On the other hand, physical examination may reveal no abnormality, as was the case with 16 patients in this series. Clubbing of the fingers was not observed even in the presence of other chronic pulmonary disease, and it has been described only once in the literature.[24]

The laboratory data are occasionally helpful. The leukocyte count and the erythrocyte sedimentation rate are not affected by the oil pneumonia per se, although they may be increased by secondary pulmonary infection or by the underlying illness. The presence in the sputum of oil globules, either intracellular or extracellular, is a diagnostic aid provided liquid petrolatum can be identified chemically or by differential staining, but frequently no sputum is available. Since false positive results may be obtained in the case of any person who has recently taken oil, it is advisable to withhold all oily medication for several days before examination of the sputum is to be attempted.

The roentgen findings are of importance in the diagnosis. In the early stages the markings in the lower lung fields are exaggerated. As the lesions progress, linear and nodular infiltrations develop until finally areas of consolidation are formed. These are almost always situated at one or both pulmonary bases. They usually lie close to the cardiac shadow and extend from the hilus to the diaphragm. Rarely the process first appears in one of the upper lobes, although if administration of oil is continued the lower lobes are eventually affected. When the parenchyma is more extensively involved, infiltration may be seen extending into the infraclavicular regions. The lesion may appear as an

24. Ellinger, E.: Paraffinölschädigung der Lunge, Fortschr. a. d. Geb. d. Röntgenstrahlen **57**:84 (Jan.) 1938.

irregular mottling composed of linear and nodular infiltrations or as a dense, homogeneous consolidation. Serial roentgenograms may show no changes for years other than gradual shrinkage of these areas due to progressive fibrosis. Compensatory emphysema may occur in the uninvolved parenchyma of the lung. Enlargement of hilar shadows is not as prominent in adults as it seems to be in children, despite the fact that oil may be found in the hilar lymph nodes.

When secondary infectious bronchopneumonia complicates the picture the roentgen appearance is apt to be confusing. At this time the shadows are a combination of the basal lesions due to oil and the superimposed exudative reaction due to the infection, which may involve other lobes as well. In addition, pleural effusion may be present. As the process subsides the basal lesions become more distinct, persisting after the bronchopneumonic infiltrations have disappeared.

Oil aspiration pneumonia is readily confused with other chronic pulmonary lesions, particularly those involving the lower portions of the lungs. Some of these require definite therapy or affect the prognosis, and it therefore becomes important to differentiate them as far as possible. In our experience lesions due to oil have been mistakenly diagnosed as bronchiectasis, unresolved pneumonia, pulmonary metastasis, primary tumor of the lung, infarct and tuberculosis.

The clinical and roentgen appearance of bronchiectasis may be similar to that of oil pneumonia. The sputum in the former, however, is more profuse and is often foul; clubbing of the fingers is frequently present, and roentgen study with iodized poppyseed oil reveals dilated bronchi. The two conditions may, of course, coexist. Unresolved pneumonia and chronic pneumonitis of infectious origin are difficult to distinguish from the condition due to oil. It is probable, in fact, that oil is actually the cause of a considerable percentage of such lesions for which the etiologic agent has never been established.

A considerable number of our patients had malignant tumor elsewhere than in the lungs. Pulmonary shadows were likely, therefore, to be improperly interpreted as due to metastasis, particularly as the roentgen appearance may be similar. Failure of the pulmonary infiltrations to increase in size over a period of months after intake of oil has been stopped is strong evidence against a diagnosis of metastasis.

Primary pulmonary neoplasm may also be incorrectly diagnosed because of the fact that it may be indistinguishable roentgenographically and even on gross pathologic examination from oil aspiration pneumonia (particularly the advanced stages). The course of the two processes differs, however, and in most instances repeated roentgen examinations supplemented by bronchoscopic examination and biopsy will serve to differentiate them.

Shadows in the lower portions of the lungs in persons with cardiac disease may, of course, be attributable to pulmonary infarcts. Blood-

streaked sputum and sudden dyspnea in such patients favor this diagnosis. More important, however, is the fact that shadows due to infarct are usually evanescent, quickly diminishing in size; infarcts may become organized, but this is rare.

Basal tuberculosis is relatively uncommon and is almost always attended by pulmonary symptoms. On the other hand, oil aspiration pneumonia is most often present in the lower lobes and usually produces few or no symptoms. When the lesion caused by the oil is extensive and involves the upper lobes or begins in an upper lobe, differentiation may be difficult. The presence of cavitation and the demonstration of tubercle bacilli in the sputum establish the diagnosis of tuberculosis; sputum negative for tubercle bacilli in the presence of large infiltrations attended by fever or other evidence of activity practically always rules it out. In general, tuberculosis is less often a source of confusion in the cases of adult patients than might be expected.

It cannot be too strongly emphasized, however, that oil pneumonia is frequently associated with these other pulmonary diseases, and in such cases differential diagnosis may be extremely difficult.

The following case histories are presented at length because of their unusual interest. The first 4 cases reported were studied post mortem; the remaining 2 were studied clinically only.

REPORT OF CASES

CASE 1.—M. C., a man aged 45, was admitted to the hospital in April 1922 with multiple sclerosis of many years' duration. He had progressive bulbar involvement and dysphagia. From 1931 to 1936 he received liquid petrolatum by mouth several times weekly. In January 1933 he had an episode of dyspnea and cough, his temperature rising to 103.6 F. This lasted three days. In December 1934 a second episode of productive cough and fever, with temperatures to 102.6 F., occurred; this episode lasted for seven days. At this time, dulness, bronchial breathing and rales were demonstrable bilaterally, while roentgen examination (fig. 2) revealed diffuse, mottled density made up of coalescent exudative patches involving the major portions of both lungs. No subsequent roentgenograms were taken. In February 1935 a third episode of fever occurred, with temperatures to 101 F., and lasted three days. A chronic nonproductive cough developed in November, and the man died three months later, in February 1936.

At autopsy there was massive, firm consolidation of all lobes with obliteration of fissures. On cut section the lung tissue was yellow-brown to gray-white and was spongy. Microscopic examination revealed all stages of oil pneumonia, the moderately advanced stage predominating. Oil was present in the hilar nodes.

Comment.—This case illustrates massive involvement of the lungs with death probably resulting from gradual asphyxia. Dysphagia of nervous origin was the predisposing factor. Although necropsy showed no evidence of secondary infection, it is reasonable to assume that the febrile episodes were due to bronchopneumonia. Early recognition of

the condition and discontinuance of the medication might have prolonged the life of the patient.

CASE 26.—A. H., a man aged 60 with hypertensive cardiac disease was admitted to the hospital in August 1937. He had undergone 2 "nasal sinus operations" six years previously and had been using nose drops (ephedrine in oil) daily for many years. While he was in the hospital this medication was continued, together with administration of liquid petrolatum by mouth almost every day. Physical examination on admission revealed bilateral basal rales and persistent loud bronchial breathing at the base of the left lung. Repeated roentgen examinations showed irregular areas of consolidation in the lower lobes of both lungs, close to the cardiac shadow and extending to the diaphragm; these were interpreted as due to infarction or bronchiectasis. The patient had a persistent dry cough, and his

Fig. 2 (case 1).—Unusually extensive oil pneumonia associated with secondary infectious bronchopneumonia.

temperature was frequently elevated to 101 F. In April 1938 he complained of a sudden pain in the left side of the chest and became cyanotic and dyspneic. His temperature rose to 102 F., and he died several hours later.

At autopsy firm consolidations were present in the middle and lower lobes of the right lung and in the lower lobe of the left lung. These areas contained strands of pale fibrous tissue and exuded oil on pressure. The right pleural space was obliterated. Bronchiectasis was present in the lower lobes of both lungs. There was a massive gelatinous lobar consolidation in the upper lobe of the left lung, evidently the cause of death. Microscopic study of the middle lobe of the right lung and the lower lobes of both lungs revealed moderately advanced to advanced stages of oil aspiration pneumonia. Microscopic study of the upper lobe of the left lung revealed a picture typical of early lobar pneumonia. Oil was present in the hilar nodes.

Comment.—In this case the condition was complicated by bronchiectasis, which was probably responsible for the persistent fever and, in part at least, for the cough. The puzzling thoracic findings and the history of prolonged self medication with oily nose drops should have suggested the diagnosis of oil pneumonia and brought about discontinuance of the medication. Instead, repeated aspiration of infected oil continued to carry infection into a lung already congested because of cardiac failure and little able to resist, thus undoubtedly contributing toward a fatal outcome.

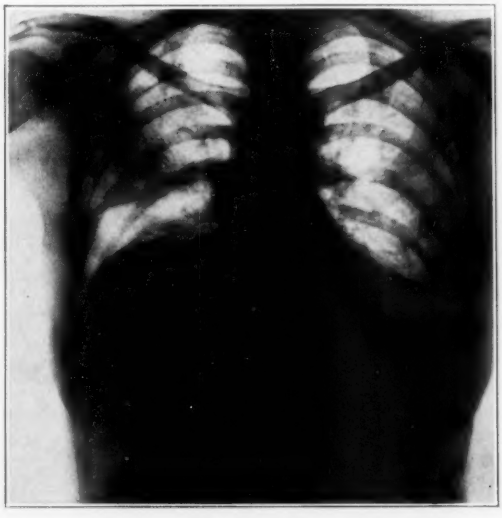

Fig. 3 (case 27).—Oil pneumonia involving the upper lobe and the mesial portion of the base of the right lung. There are thickening of the right transverse fissure and elevation of the diaphragm.

CASE 27.—L. K., a woman, aged 42, was admitted to the hospital in September 1909 with extensive scleroderma. She had considerable difficulty in opening her mouth and was forced to eat with her head tilted far back. She received 30 cc. of liquid petrolatum daily by mouth from 1924 to 1928, petrolagar daily from 1928 to 1930 and cod liver oil and liquid petrolatum frequently from 1930 to 1934. In February 1927 she had a cough with fever, the temperature rising to 104 F.; this episode lasted four days. A roentgenogram of the chest taken at this time revealed consolidation involving the lower two thirds of the upper lobe of the right lung. In July 1930 she had pain in the right side of the chest, accompanied by a persistent nonproductive cough; physical examination revealed dulness, bronchial breathing and rales on the right. These signs persisted, appearing to a lesser degree at the base of the left lung. Pleural effusion developed on

several occasions, but the material was repeatedly sterile on culture and negative for tubercle bacilli by guinea pig inoculation. A tuberculin test elicited a negative reaction. Thoracic roentgenograms (fig. 3) were taken on several occasions between 1930 and 1934; all revealed mottling and fibrosis in the lower two thirds of the upper lobe of the right lung, indicating nonresolution of the pneumonic consolidation seen in the 1927 film. Infiltrations gradually appeared in the right lower lobe, close to the cardiac shadow and extending to the diaphragm. The patient had several episodes of fever, the temperature rising to 102 F., and died in October 1934, during one of them. The prevailing clinical diagnosis was chronic pneumonitis, although diagnoses of tuberculosis and pulmonary neoplasm were considered for some time.

At autopsy firm gray consolidations were present in adjoining portions of the upper, middle and lower lobes of the right lung, with pale fibrous strands throughout. Numerous pleural adhesions were present, as well as purulent bronchiolitis. Microscopic examination revealed an advanced stage of oil aspiration pneumonia, chiefly paraffinoma.

Comment.—Although the early clinical picture as well as the roentgen evidence strongly suggested tuberculosis, repeated bacteriologic studies failed to bear this out. A diagnosis of tumor of the lung could not long be seriously considered because of the protracted course. Familiarity with the existence of oil aspiration pneumonia as a disease entity, together with the long history of intake of oil, the presence of an obvious predisposing factor and the clinical and roentgen evidence of chronic pneumonitis, should have suggested the correct diagnosis. The symptoms are readily explained by the presence of purulent bronchiolitis and repeated bronchopneumonic episodes. Of particular interest is the initial involvement of the lower portion of the upper lobe of the right lung, probably the result of the position that had to be assumed for eating.

Case 41.—S. M., a man aged 56, was admitted to the hospital on Feb. 20, 1936 with degenerative cerebellar disease, pseudobulbar palsy and dysphagia. From the time of his admission until three months before his death he received liquid petrolatum by mouth several times weekly. A roentgenogram of the chest taken on admission revealed clear pulmonary fields. In August 1937 he had a nonproductive cough, pain in the chest and fever, the temperature rising to 104 F.; this episode lasted six days. Dulness, increased fremitus and rales were present at the bases of both lungs. The leukocyte count was 14,400 per cubic millimeter, with 78 per cent polymorphonuclears. A roentgenogram of the chest at this time revealed pneumonic consolidation close to the cardiac borders in the lower lobes of both lungs, together with scattered infiltrations in the upper lobe of the right lung. One month later, during an afebrile period, the physical signs were still present; roentgen examination (fig. 4) revealed persistence of the consolidation in the lower lobes, the right upper pulmonary field having cleared. A second acute episode occurred in May 1938, the temperature rising to 103 F. and remaining elevated for eight days. A roentgenogram of the chest revealed another area of consolidation in the upper lobe of the right lung, together with an increase in extent of the infiltrations in the lower lobe of the left lung. Another film, taken in October, revealed increasing consolidation throughout the right lung. In

order to rule out chronic suppurative pneumonitis on a bronchiectatic basis, bronchographic examination was performed on November 4; the bronchial tree was found to be normal. By November 21, evidence of iodized poppyseed oil could no longer be detected on the roentgenogram. At this time a diagnosis of oil aspiration pneumonia was made, and administration of liquid petrolatum was stopped. Examination of the sputum in January 1939 revealed oil droplets. On January 18 the patient again had a high fever, and an increase in the amount of consolidation was seen in the lower lobes of both lungs. Death occurred on January 20.

At autopsy extensive, firm gray areas of consolidation were observed in the upper, middle and lower lobes of the right lung, and in the lower lobe of the left lung. Oil-containing fluid could be expressed from the involved portions; the oil

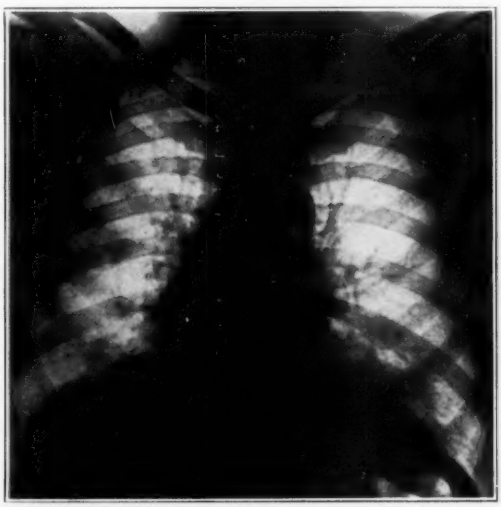

Fig. 4 (case 41).—Oil pneumonia. The roentgenogram shows the basal consolidations during afebrile stage.

was chemically identified as liquid petrolatum. The upper lobe of the left lung was congested, and the hilar nodes were enlarged. Microscopically the appearance of the lesion varied from that of the moderately advanced to that of the far advanced (paraffinoma) stage. Moderate bronchopneumonia was present.

Comment.—This case has several interesting features. The oil aspiration pneumonia developed while the patient was in the hospital, and the progress of the lesion was followed by roentgen examination throughout his illness. Recurrent episodes of secondary bronchopneumonia marked the clinical course; during these, symptoms referable to the lung appeared. The correct diagnosis was made clinically, although too late for the cessation of administration of oil to be effective in

changing the outcome. It is also of interest to note that iodized oil introduced into the bronchi was eliminated in spite of the extensive lesions produced by liquid petrolatum.

CLINICAL CASE 1.—A. W., a man aged 20, was admitted to the hospital on Nov. 9, 1936, with multiple sclerosis and resultant dysphagia. He received 30 cc. of liquid petrolatum by mouth three to four times weekly. A roentgenogram of the chest taken in January 1937 revealed a few scattered linear infiltrations in both lower lung fields. These were not considered clinically significant. In August 1938 the patient became acutely ill with chills, fever and respiratory difficulty; this episode lasted several weeks. The course was septic, with wide fluctuation of the temperature, which often reached 105 F. In September signs of diffuse bronchopneumonia appeared in both lungs. On September 12 a roentgenogram of the chest revealed small areas of consolidation scattered rather uniformly throughout all the lobes; this was thought at the time to represent either disseminated bronchopneumonia or hematogenous tuberculosis. The tuberculin test elicited a negative reaction, and the sputum contained no tubercule bacilli on repeated examination. The leukocyte count was 28,800 per cubic millimeter, with 84 per cent polymorphonuclears. On November 21, about six weeks after all significant fever had abated, roentgen examination showed persistence of the infiltrations throughout the lower half of the right lung and throughout the lower lobe of the left lung, most marked close to the heart. A diagnosis of oil aspiration pneumonia with superimposed secondary bronchopneumonia was made at this time. All oil medication was stopped. Follow-up roentgenograms of the chest taken as late as March 30, 1939 revealed little, if any improvement. The consolidation persisted but took on a distinct fibrous character. At present the patient is afebrile and has no symptoms referable to the respiratory tract other than a little respiratory difficulty attributable in part to disturbance in innervation of the muscles of the chest.

Comment.—This case in the early roentgen manifestations closely simulated that of M. C. (case 1, postmortem group). The persistence of pulmonary shadows in a patient with dysphagia receiving liquid petrolatum justifies the diagnosis of oil pneumonia. As would be expected, the infiltrations have become distinctly fibrotic since discontinuation of the oil treatment.[25]

CLINICAL CASE 4.—E. F., a woman aged 37, was admitted to the hospital on Jan. 3, 1939, with congenital bilateral athetosis and dysphagia. She received no oily medicaments in the hospital, but she had been taking 1 tablespoonful of liquid petrolatum twice daily for many years. At no time had she had any fever or symptoms which would indicate pulmonary disease. Roentgen examination of the chest on January 10 (fig. 5) revealed an area of consolidation occupying the cardiohepatic angle of the right lower lung field; a similar lesion was present in the mesial portion of the lower lobe of the left lung. Roentgen follow-up two months later showed no change, but physical examination of the chest did not disclose any abnormalities. The sedimentation rate was normal.

Comment.—This case is presented because it demonstrates all the essential features which make the diagnosis of oil aspiration pneumonia

25. Since this paper went to press, the patient died, after an ascending urinary infection. The diagnosis of oil aspiration pneumonia was confirmed at autopsy, and liquid petrolatum was identified in the lung.

possible; namely, dysphagia, a long history of intake of oil, roentgen demonstration of persistent, unchanging consolidations characteristically situated in the mesial portions of the bases of both lungs and complete absence of clinical evidence of pulmonary disease.

GENERAL COMMENT

It is evident from the number of cases presented here that oil aspiration pneumonia is by no means as uncommon in adults as was previously thought. Its occurrence requires only the oral, nasal or intratracheal administration of oil and, in many instances, particularly when the oral route is employed, the existence of some predisposing factor

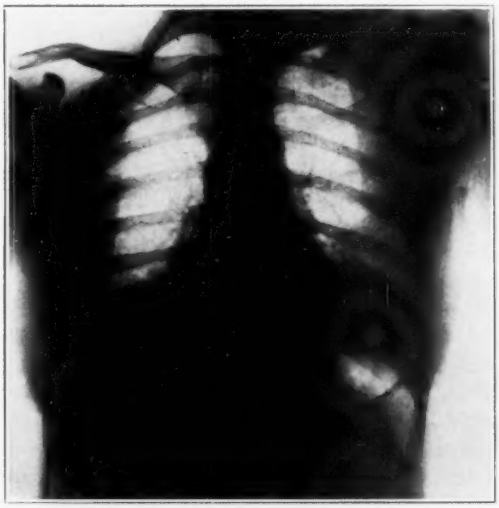

Fig. 5 (clinical case 4).—Oil pneumonia. There are consolidations at the mesial portions of both pulmonary bases. There is no clinical evidence of pulmonary disease.

favoring its aspiration. Most of our patients were elderly, debilitated persons suffering with other and incurable disease. A smaller and younger group had dysphagia associated with some nervous disorder. A few patients had oral pathologic conditions which interfered with opening the mouth, chewing and swallowing. Several had nasal disease of one type or another necessitating the habitual use of intranasal medication. Finally, some had no evident predisposing condition whatever.

Liquid petrolatum was by far the most important etiologic agent, and the paucity of instances in which the pneumonia was attributable

to oils other than this, both in the cases of adults reported in the literature and in our own series, is noteworthy. Fats and oils of animal origin, such as cod liver oil and milk fat, are not forcibly administered to adults as they frequently are to weak and debilitated infants, who have, therefore, far more opportunity to aspirate such substances. Since animal oils may be extensively hydrolyzed in the lung and since both the macrophagic and the proliferative reaction are by no means as prominent as they are with liquid petrolatum, it is possible, however, that a few bona fide instances may have been overlooked or misinterpreted as simple or terminal aspiration bronchopneumonia.

Unless the pulmonary lesion produced by liquid petrolatum is so extensive that the patient dies of asphyxia, as occurred in 1 of our cases, it cannot of itself be considered a direct cause of death. Usually the patient may live for an indefinite period, until finally carried off by his primary disease or by secondary infection. Purulent bronchiolitis and bronchitis, bronchiolectasis and occasionally bronchiectasis and recurring episodes of bronchopneumonia, however, may be concomitant conditions over a considerable period. The general diminution in resistance occasioned by the debilitated state of the patient (a fact responsible for the frequency with which terminal bronchopneumonia complicates any type of chronic disease) is in part responsible for this high incidence. Other factors, however, make patients with oil pneumonia particularly susceptible to secondary bacterial invasion: the repeated aspiration of oil and other infected material and the serious interference with the normal self-cleansing action of the lung brought about by choking of the macrophages with oil, the blockage of the lymphatics, the disturbed ciliary action, the increasing fibrosis and, in some cases, the underlying chronic passive congestion.

Uncomplicated oil aspiration pneumonia is practically asymptomatic, and physical findings are of little differential value. Diagnosis of the condition must, therefore, depend on the roentgen appearance and on the history of intake of oil, often coupled with some known predisposing factor. The presence of persistent pulmonary consolidations with disproportionately slight symptoms or of infiltrations which do not fit into any well established disease pattern should suggest oil pneumonia. If the condition is kept in mind, its diagnosis is not likely to be particularly difficult.

It must be emphasized that administration of oil even in the presence of predisposing factors does not necessarily mean that oil pneumonia will occur. Liquid petrolatum is widely used without evident harm, especially by elderly persons, who are likely to have chronic pulmonary disease of other origin. We know of several dysphagic patients who

have been receiving oil but in whom no evidence of oil pneumonia has been found.

By the same token, the fact that such a condition may occur in no way warrants discontinuance of the use of liquid petrolatum except, perhaps, in the nose, where it apparently serves no useful purpose. It must be realized, however, that its use is not without potential danger and that its promiscuous use by debilitated or dysphagic persons should be discouraged. Certainly, considering the total number of persons who utilize this oil, the incidence of the disease is very low indeed. It is, of course, impossible to estimate how frequently small quantities may be aspirated and adequately disposed of by expectoration and absorption as in the case of iodized poppyseed oil. Resorption of well developed lesions is believed to be not infrequent in infants, although in such cases other oils and fats are usually involved. This was not observed in any of our patients. Such reports are necessarily based on roentgen observations and cannot be corroborated. It would seem to us, in view of the pathologic process involved, that very early small lesions may be capable of resolution under good conditions but that disappearance of a lesion in the type of person in whom it is usually found is not likely to occur.

SUMMARY AND CONCLUSIONS

Oil aspiration pneumonia occurs more frequently in adults than is generally believed. A group of 47 cases with 41 autopsies is presented. All the patients were adults.

Oil pneumonia is a chronic pulmonary condition caused by aspiration of oil, usually repeated over a period of time. Liquid petrolatum is by far the most important etiologic agent in the adult.

The oil may be administered orally, intranasally or intratracheally. In this series the oral route was found to have been the one most often employed.

Aspiration is favored by the bland, nonirritating character of the oil. When the oral route is used, dysphagia and debilitated states are additional important predisposing factors.

The condition is often practically asymptomatic, and physical findings are of little differential value. Most symptoms and signs, when present, are due to superimposed infection, which is common. Diagnosis must depend on the roentgen findings, a history of intake of oil and often some known predisposing factor; occasionally oil droplets in the sputum may be identifiable and are of aid.

Persistent pulmonary infiltrations (particularly those involving the mesial portions of the pulmonary bases) which are accompanied by disproportionately few symptoms, which are more extensive than the clinical

appearance of the patient would seem to indicate or which do not fit into any well established disease pattern, should suggest oil pneumonia.

Prognosis as to life is good so far as the oil pneumonia itself is concerned; death usually results from secondary infection or from the underlying primary illness.

The use of liquid petrolatum, particularly when self administered, is not without potential danger. Its promiscuous use intranasally and by the oral route by debilitated or dysphagic persons should be discouraged.

Dr. Max Pinner, of the Division of Pulmonary Diseases, made many valuable suggestions for this study.

BRONCHOGENIC CARCINOMA

WITH SPECIAL REFERENCE TO RESULTS WITH ROENTGEN THERAPY

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AND
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The increasing interest in carcinoma of the lung, which has been aroused by the rising incidence of that disease during the past three, and especially the last two decades, has brought forth many publications concerning its various features. The clinical, diagnostic, pathologic and therapeutic aspects have been classified by a number of competent observers. Recently Simons [1] in his excellent monograph "Primary Carcinoma of the Lung" exhaustively surveyed the present kowledge and opinions about bronchogenic carcinoma.

There is little or nothing new which we can add to the clinical manifestations and diagnosis of the disease from our own experiences with a fairly large group of patients. Our experiences essentially substantiate the observations of others. The data obtained on 88 patients, as shown in tables 1 to 6, are presented to round out our report and add whatever weight they may to what has already been said, rather than to raise new issues. But since we want to discuss the diagnosis in greater detail, a few of our symptomatic observations, and only those not stressed by others, may be mentioned as diagnostically important. Table 2 shows a high incidence of the symptom of loss of weight. With the success of the treatment of pulmonary cancer depending so much on an early diagnosis, that is, on diagnosis at least during the premetastatic stage, we should record that a considerable loss of weight, let us say 20 pounds (9.1 Kg.) or more, usually signifies the presence of abdominal metastases. The tumor on the lung alone has not been seen to cause much loss in weight unless abscess formation has set in. Chronic hoarseness, which we found in 10 per cent of our patients, almost always means envelopment of the laryngeal nerve by the tumor mass and signifies a mediastinal invasion which is likely to render surgical

Read before the Chicago Society of Internal Medicine, April 24, 1939.

From the School of Medicine of the Division of Biological Sciences, University of Chicago.

1. Simons, E. J.: Primary Carcinoma of the Lung, Chicago, The Year Book Publishers, Inc., 1937.

therapy futile. The significance of this symptom is enhanced if examination also reveals paralysis of the diaphragm. In general, and with reference to the demand for early diagnosis, it can be said that the presence of a great number of symptoms means advanced neoplasm, that the smallest tumor causes the fewest symptoms and that therefore the task of early diagnosis of malignant tumor of the lung requires finer work than the skilful investigation only of the most pronounced symptoms, those which cause the average patient to seek medical aid.

TABLE 1.—*Age Distribution*

Age	Number of Patients	Per Cent of Total
30-40	3	3.4
40-50	32	36.3
50-60	31	35.2
60-70	12	13.6
70-80	9	10.2
80-90	1	1.1
	88	
Youngest patient	32	
Oldest patient	82	

TABLE 2.—*Incidence of Predominant Symptoms*

Symptom	Number of Patients with Symptom
Cough	67
Sputum	54
Pain in chest	51
Dyspnea	32
Hemoptysis	30
Loss of weight	59
Fatigue	36
Anorexia	21
Chills and fever	15
Symptoms referable to involvement of central nervous system	13
Hoarseness	9

The chief purpose of our report is a short comment on certain therapeutic aspects of the disease. Here, experiences have not been so uniform, and opinions are not so unanimous. With the increasing acceptance of the disease as a frequent occurrence by the medical and lay public, there has been a steadily growing conception that this kind of cancer is cured by irradiation, chiefly by roentgen therapy. This belief has become so widespread that patients in whom the disease has been diagnosed elsewhere, or merely suspected, are referred to institutions equipped for roentgen therapy, not for their confirmation of the diagnosis nor for therapeutic advice, but simply with a request for roentgen therapy. On the other hand, there are a good many investigators who doubt the value of irradiation and some who disclaim all

favorable results. Of the latter group, the strongest opinion was expressed by Graham [2] as follows:

There is no record in the literature of the successful treatment by radiotherapy of a single case in which the pathologic evidence has been incontrovertible and in

TABLE 3.—*Site of Tumor*

	Right Lung	Left Lung
Large bronchi		
Main bronchus	5	5
Upper	13	9
Middle	4	..
Lower	3	3
Undetermined	22	5
	47	22
Peripheral location	11	8
	58	30
Total number of patients	88	

TABLE 4.—*Site of Metastasis*

	Clinical Observations	Postmortem Observations
Lymph nodes:		
Cervical	8	4
Tracheobronchial	..	14
Axillary	..	1
Mesenteric	1	..
Long bones	8 (?)	..
Vertebrae	3	3
Skull	..	1
Ribs	..	7
Chest wall	2	..
Pelvis	..	4
Pleura	8	11
Lung (opposite)	..	5
Heart	..	1
Pericardium	..	3
Stomach	..	1
Colon	..	1
Liver	3	9
Pancreas	..	3
Kidneys	..	2
Spleen	..	1
Bladder	1	1
Peritoneum	..	8
Adrenal glands	..	10
Pituitary gland	..	1
Thyroid	..	1
Central nervous system	5	2

which a five year interval without recurrence has elapsed between the treatment and the time of reporting the case, despite the fact that many cases have been treated according to the most modern method of using both x-rays and radium. It would seem, therefore, that unless some entirely new general principle in the treatment of carcinoma is advised, the only method which can at present offer any hope is the wide surgical removal of the tumors and surrounding tissues.

2. Graham, E. A.: Primary Carcinoma of the Lung or Bronchus, Ann. Surg. **103**:1, 1936.

In view of the controversy, we felt that we should examine and scrutinize our own experience in the chest division of the School of Medicine of the Division of Biological Sciences, University of Chicago, especially since we are neither surgeon nor roentgenologist and since we are not inclined by training toward either method of therapy.

Since the evaluation of any treatment rests with the dependability of the diagnosis, the most rigid diagnostic standard needs to be applied

TABLE 5.—*Data with Reference to Diagnostic Proof*

Specimens studied at biopsy		35
Primary tumor (bronchoscopy)	20	
Cervical lymph nodes	8	
Central nervous system (craniotomy)	3	
Chest wall	2	
Inguinal lymph nodes	1	
Pleural fluid	1	
Specimens studied post mortem		33
Total histologically proved		68
Clinical and roentgen observations accepted as sufficient for diagnosis		20
Total		88

TABLE 6.—*Duration of Life After Onset of Symptoms*

Duration of Life in Months	No. of Patients Without Roentgen Therapy	No. of Patients With Roentgen Therapy
1- 6	10	12
6-12	15	10
12-24	7	11
24-48	2	2
48-60	1	1
Total patients dead	35 (75.2%)	36 (85.7%)
Result unknown	9	4
Patients still living	2*	2†
Total	46	42

* One patient was living for seventeen months and 1 for twenty-two months.
† One patient was living for two months (therapy incomplete) and 1 for thirty months (pneumonectomy three months after the onset of symptoms was followed by roentgen therapy).

in a disease for which cures have been claimed for generations and in all parts of the body, when carcinoma may not have existed at all. As proof of a malignant neoplasm, only a microscopic examination with positive results can be accepted. The 88 patients studied, for whom data with reference to diagnostic reliability are presented in table 5, were chosen after elimination of a considerable number whose hospital diagnosis was considered as insufficiently proved. For 68 of the accepted patients the diagnosis was proved histologically, the proof for about half being obtained by the taking of a biopsy specimen either from the primary tumor by way of the bronchoscope or from extrapulmonary

metastases; for the other half the proof was obtained through post-mortem examination only. For 20 patients the diagnosis was considered as clinically established although the histologic proof was lacking. We included those patients who presented a suggestive anamnesis in combination with characteristic physical signs and, most of all, roentgenographic evidence and who remained under our observation, some until death. The evidence thus gained by an experienced observer can be convincing and even overwhelming. We may mention only the presence of a hemorrhagic pleural effusion, which is almost pathognomonic for malignant neoplasm. Not to consider such patients as having pulmonary neoplasm would be doing injustice to the possibilities of clinical and roentgenographic interpretation and would lead to serious consequences for patients who have no metastases and whose primary

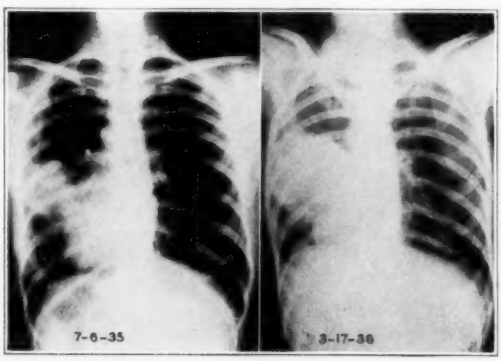

Fig. 1.—Roentgenograms of a patient showing growth of a peripheral tumor without demonstrable atelectasis.

growth is not accessible through the bronchoscope. We fully realize that the emphasis should be on the examining physician's special knowledge and experience with tumor of the lung. Since roentgenographic evidence is, next to tumor tissue itself, by far the outstanding diagnostic demonstration, we have illustrated the most characteristic features and some of the changes, indicating the periods of development (figs. 1 to 4). The most essential factor in the development and the variability of this evidence is the degree of bronchial occlusion, if any, which is caused by the tumor. It determines the degree of secondary atelectasis and largely determines the degree of secondary abscess formation in the lung, which may dominate the roentgenogram. The bronchial occlusion can frequently be directly demonstrated by bronchography.

In the presentation of the results with roentgen therapy, we disclaim all technical knowledge of roentgenology. There is evidence, however, that experience and equipment, as they have been developed during the past decade or so, were progressively and skilfully applied to our patients by the roentgen specialists to whom they were referred for treatment. The dose ranged from about 1,200 to 16,000 roentgens. The wide range is explained by the increasing recognition of the inefficiency of weak irradiation. This tendency to increase the dose appears

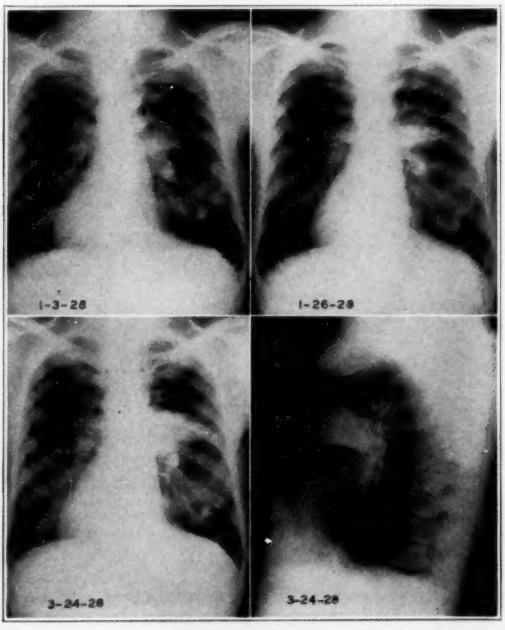

Fig. 2.—Roentgenograms of a patient showing development of wing-shaped atelectasis, with some interlobar pleuritis in the base of the right upper lobe, from carcinoma of a large secondary bronchus.

in all reports, and the results obtained in our institution and elsewhere can be viewed on a fairly equal basis. Table 6 illustrates that in the various age groups the duration of life after the onset of symptoms in the patients who were treated was about the same as in the untreated patients. By comparison of the total groups, there is practically no difference. As a curative treatment, roentgen therapy was a complete failure, since the mortality was not diminished and the duration of life

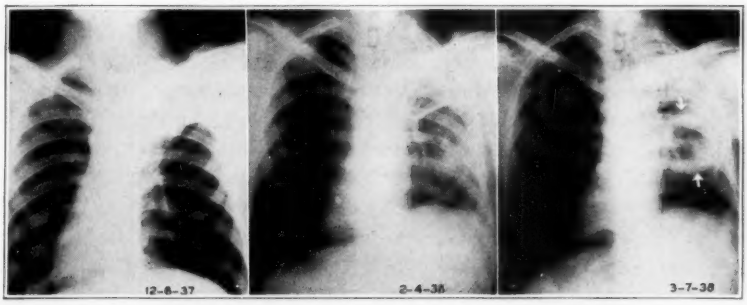

Fig. 3.—Roentgenograms of a patient showing, first, massive atelectasis from carcinoma of the main bronchus of the right upper lobe; second, obstruction of the bronchus of the middle lobe with residual atelectasis, and third, subsequent abscess formation there.

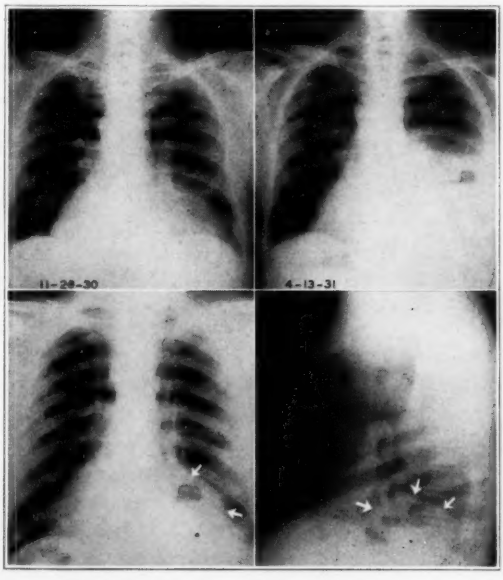

Fig. 4.—Roentgenograms of 2 patients, the upper two pictures showing atelectasis due to carcinoma of the bronchus of the right lower lobe resulting in abscess formation, and the lower two showing abscess formation within the tumor itself (frontal and lateral views), with no demonstrable atelectasis. Note the diffuse outline of the area in the upper films and the sharply circumscribed shadow of the tumor in the lower.

not prolonged. As Steiner [3] pointed out in his paper, the destructive effect observed on histologic examination stayed much below what could be expected to annihilate the tumor, even when large doses had been given. Clinically, there may be an effect in the form of some symptomatic relief which is caused by a release of bronchial occlusion and clearing of atelectasis following some shrinkage of the tumor. Only 3 patients of our own group reported disappearance of symptoms. How unjustified it is to relate mere symptomatic improvement to roentgen therapy is illustrated by the instance of a patient who had been seen at another clinic in our institution in November 1937 and on the basis of roentgenographic observations was advised to have roentgen therapy at home, away from Chicago. When we recalled him for the purpose of this study in March 1939, he disclaimed all symptoms. According to

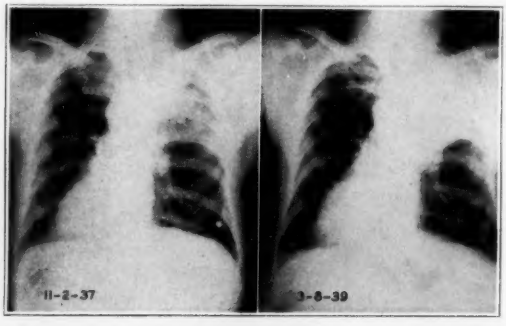

Fig. 5.—Roentgenograms of a patient showing unfavorable progress of untreated endobronchial carcinoma, accompanied by temporary gain in weight and symptomatic improvement.

his information he had gained 35 pounds (15.9 Kg.) from the lowest weight following the examination in 1937. Our own records showed a gain of 16 pounds (7.3 Kg.). He asserted that, against advice, he had not taken irradiation or any other therapy. Physical and roentgenographic examination of the chest revealed a considerable increase of evidence of carcinoma (fig. 5). Bronchoscopic examination was then made, and a biopsy specimen taken from a friable tumor mass in the right upper bronchus showed a squamous cell carcinoma.

Whatever roentgen changes can be observed also seem to be due to the clearing of atelectatic areas rather than to an essential destruction of the tumor. We found such changes in only 2 patients, whose roent-

3. Steiner, P. E.: Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of Lung, Arch. Int. Med., this issue, p. 140.

genograms are shown in figure 6. These patients, 1 of whom has previously been reported by Steiner and Francis [4] as having a "superior pulmonary sulcus tumor," had been treated with 7,700 and 8,800 roentgens, respectively. How insignificant the effect on the tumor itself was can be judged by the fact that 1 of the patients died one week and the other, six weeks, after the films showing the clearing in the pulmonary field had been taken.

We cannot agree with the authors who maintain that extensive roentgen therapy should be attempted in any case, although it may not

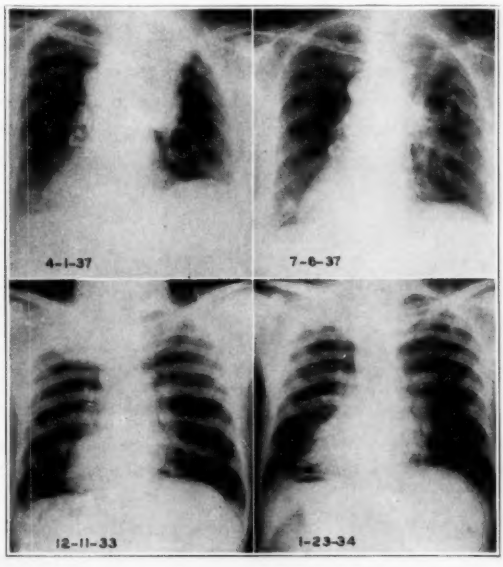

Fig. 6.—Roentgenograms of 2 patients showing clearing of atelectasis due to shrinkage of tumor following roentgen therapy.

hope to be curative, since no serious ill effects occur. We found the effects from hard irradiation considerable—nausea, abdominal distress, severe headaches, general weakness and malaise being frequent and of considerable degree. The depleted blood stream has to be replenished by blood transfusions. The patient with hopeless pulmonary neoplasm dies an easier death without treatment, and the suggestion of roentgen therapy for psychologic reasons alone, it seems to us, is not in order.

4. Steiner, P. E., and Francis, B. F.: Primary Apical Lung Carcinoma, Am. J. Cancer **22**:776, 1934.

Our own search of the literature resulted in nearly the same experience as did Graham's. In most cases of reported cures, no serious proof of diagnosis is offered. In others, the evidence is insufficient. In spite of our contention that an acceptable diagnosis may be made by clinical and roentgenographic evidence only, i. e., a diagnosis sufficient for a plan of therapy, we would not undertake to report such patients as cured by any therapy without further diagnostic evidence. We have, however, no such patients, since of the 20 whom we included in that group, 15 have died, and the fate of 5 is unknown. There is reason to assume that the latter have died, too. This alone suggests the accuracy of the clinical and roentgenographic diagnosis.

The duration of life following the diagnosis may be considerable without any treatment (fig. 5). Periods of survival of five years and more have been reported. Figure 7 shows a roentgenogram

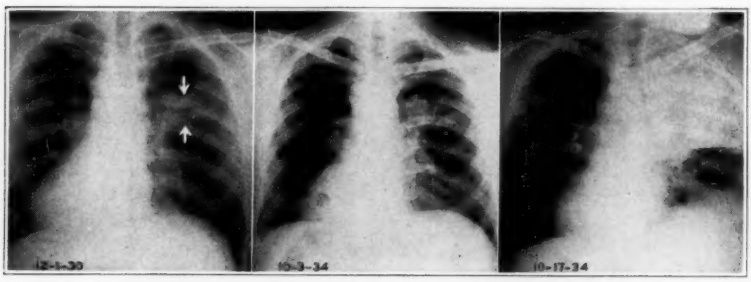

Fig. 7.—Roentgenograms of a patient showing unchanged persistence of carcinoma for nearly four years, eventually resulting in fatal occlusion pneumonia.

of a patient whose condition remained unchanged for nearly four years. Autopsy after death from an occlusion pneumonia in the dependent lung lobe showed carcinoma. It is not likely that roentgen irradiation of 4,000 r, which is now considered as insufficient, caused the long survival, especially since the lesion appeared unchanged in films of the chest. Kernan,[5] in discussion of the results of Vinson,[6a] who reported survivals of four and a half to seven years after roentgen therapy, raised the question whether the long duration of life may not have been due to the peculiarities of some tumors which act as benign adenomas, although they are classified as carcinomas histologically,

5. Kernan, J. D.: Carcinoma of the Lung and Bronchus: Treatment with Radium Implantations and Diathermy, Arch. Otolaryng. **17**:457 (April) 1933; in discussion on Vinson.[6a]

6. Vinson, P. P.: (*a*) Primary Malignant Disease of the Tracheobronchial Tree, J. A. M. A. **107**:258 (July 25) 1936; (*b*) Primary Carcinoma of the Bronchus, Minnesota Med. **15**:15, 1932.

borderline cases between benign and malignant growth. In view of this, it is interesting that all of Vinson's [6] and Vinson and Leddy's [7] favorable results were obtained in patients with adenocarcinoma.

Our comments are not meant as a sweeping condemnation and discouragement of roentgen therapy. We simply wish to record our experience that up to the present irradiation has not been able to cure bronchogenic carcinoma. This is in much contrast to the beliefs of many. It may well be possible that in the future roentgen technic will be developed to a stage where the rays can reach these radioresistant growths with sufficient force.

At present the surgical removal of operable tumors must be the treatment of choice. During the past two years the first results obtained in our institution (Adams [8]) have been encouraging, and it is to be hoped that further improvement in surgical technic and postoperative care will be able to save a considerably higher number of patients in whom an early diagnosis is possible.

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7. Vinson, P. P., and Leddy, E. T.: Roentgen Treatment of Primary Malignant Disease of the Tracheobronchial Tree, Ann. Otol., Rhin. & Laryng. **41**:1259, 1932.

8. Adams, W. E.: Pneumonectomy for Bronchogenic Carcinoma of the Lung: Report of Successful Case Sixteen Months After Operation, Illinois M. J. **74**:442, 1938.

PRIMARY TUMOR OF INFERIOR VENA CAVA, WITH CLINICAL FEATURES SUGGESTIVE OF CHIARI'S DISEASE

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Primary tumor of the vena cava inferior occurs rarely. This is indicated by the fact that in the examination of the records of 34,000 autopsies in the department of pathology of the University of Minnesota not a single report of its occurrence was encountered. Furthermore, a thorough search of the literature revealed the reports of only 4 cases.

The purpose of this paper is to report the occurrence of a leiomyosarcoma arising from and completely occluding the subdiaphragmatic portion of the inferior vena cava. The clinical and the postmortem observations in this case constitute the basis of the present study. From a diagnostic point of view the clinical picture was that of Chiari's disease (endophlebitis obliterans hepatica), except for certain vascular signs simulating those of constrictive pericarditis.

REPORT OF A CASE

L. S., a housewife aged 31, was admitted to the medical service of the University Hospitals on Oct. 17, 1938. She had previously been seen in the outpatient department on Oct. 4, 1938, at which time she complained of pain in the left side of the abdomen over a period of two years, cough of several months' duration and nausea and vomiting for two weeks. It was noted on October 4 that she had slight edema of the lower extremities as well as mild abdominal distention. On admission to the hospital her chief complaints were those of progressive enlargement of the abdomen and increasing edema of the lower extremities. The patient stated that in June 1938 a distressing cough developed after an acute infection of the upper respiratory tract. This cough persisted and at times was severe enough to be followed by vomiting. There was little expectoration, and the cough was always more severe at night. Palpitation and dyspnea on exertion had been noted since the birth of her last child, in June 1938. Aside from these symptoms, it appeared that the patient got along fairly well until four weeks prior to admission to the hospital. At that time she first noticed that her abdomen was enlarging, and shortly thereafter she began to have frequent attacks of nausea, occasionally

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with vomiting. These attacks had no apparent relation to the ingestion of food but were said to have been precipitated by slight activity. The abdomen enlarged progressively. Dyspnea, orthopnea and weakness developed. About ten days previous to her admission swelling of the ankles was noted.

The pain in the left side followed an injury to her left flank two years before. Since that time she had recurrent attacks of sharp pain in the left flank, occasionally radiating into the left groin and into the genital region. The pain was related to exertion.

Past and Family History.—The patient had had bronchopneumonia and scarlet fever in childhood. The menstrual history was normal. Her husband was a chronic alcoholic addict and was confined to the state sanatorium for the insane. The father and mother of the patient as well as a brother and sister were living and well. No family history of cancer was elicited. The patient's 5 children were living and well; her last pregnancy had terminated normally in June 1938. There had been no miscarriages.

Physical Examination.—The patient was a fairly well nourished young white woman, lying comfortably in bed. Her temperature was 97.5 F., and her pulse rate was 80. The head, eyes and mouth were normal on examination. The tonsils were present but not enlarged. Excursion of the diaphragm was limited by the distended abdomen. The pulmonary fields were clear; there were no signs of pleural effusion. The heart was not enlarged; the rate was regular and no murmurs were elicited. The heart tones were slightly diminished in intensity.

The abdomen was markedly distended. Shifting dulness was present; bulging in both flanks was noted, and a fluid wave was easily elicited. The superficial abdominal veins were slightly dilated. In the right upper quadrant a mass could be palpated which extended about 6 cm. below the costal margin in the midclavicular line. The mass was smooth and firm and was believed to be the liver.

Pelvic examination revealed a normal multiparous outlet and slight bilateral lacerations of the cervix. The internal genitalia could not be palpated accurately because of ascites. The rectum was normal. Marked pitting edema of both lower extremities was noted, with extension upward to involve the thighs. No edema of the upper extremities was noted. The radial pulse was small in volume, and on deep inspiration it became definitely diminished in amplitude (paradoxic pulse). The blood pressure was 128 systolic and 105 diastolic. The vital capacity was 2,500 cc. (normal, 3,200 cc.). Although the cervical veins were not noticeably distended, the venous pressure in the antecubital vein was recorded at 22.5 cm. of blood by the direct method (fig. 1). Because of increased venous pressure, ascites, edema, the absence of cardiac enlargement and the presence of pulsus paradoxus, a tentative diagnosis of constrictive pericarditis was advanced.

Laboratory Data.—The specimen of urine taken on the patient's admission had a specific gravity of 1.024 and was acid in reaction; no albumin was noted. In the centrifuged sediment there were approximately 4 pus cells per high power field. Subsequent examinations revealed intermittent mild albuminuria. The phenolsulfonphthalein excretion in two hours was 51 per cent. The hemoglobin value on admission was 90 per cent (Sahli); the red blood count 4,500,000, and the white blood count 9,450, with 74 per cent neutrophils, 24 per cent lymphocytes and 2 per cent eosinophils. There were 2.5 per cent of reticulocytes. The content of urea nitrogen in the blood was 8.2 mg. per hundred cubic centimeters. Determination of the plasma protein showed albumin 2.3 per cent and globulin 2.1 per cent, the total being 4.6 per cent. The sedimentation rate was 14 mm. the first hour and 40 mm. the second hour (Westergren). The average red blood cell diameter

(Bock erythrocytometer) was 7.2 microns; the hematocrit reading was 49 per cent; the mean corpuscular volume was 85 cubic microns and the mean corpuscular hemoglobin value was 31 per cent. The icterus index was 9. The Wassermann test and the Mantoux test gave negative results. Roentgen studies showed the abdomen to be normal, and a retrograde pyelogram gave essentially negative results. The film of the heart taken at 6 feet (1.8 meters) showed the diaphragm markedly elevated because of the fluid in the abdomen. No definite pathologic condition could be seen in the lungs. The heart appeared to be within normal limits as to size and shape. Roentgen examination of the gastrointestinal tract gave negative results. The esophagus was normal. The electrocardiogram showed diminished amplitude of the QRS complex in all leads, with an isoelectric T wave in lead I, and diphasic T waves in leads II, III and IV.

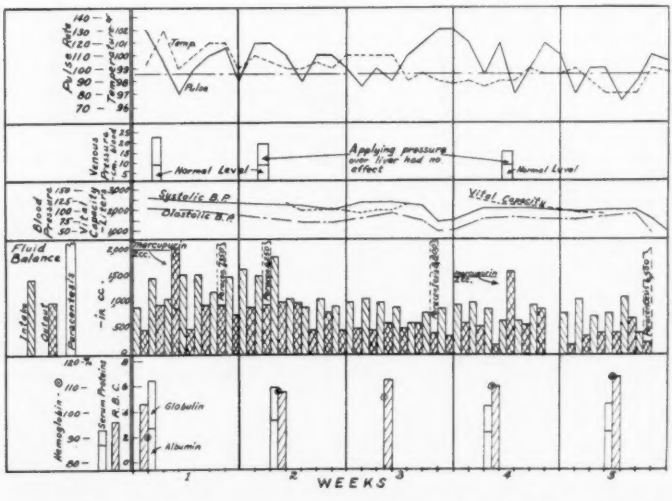

Fig. 1.—Chart showing important clinical features of occlusion of the inferior vena cava by a primary tumor (leiomyosarcoma). The pertinent features shown are the increased venous pressure in the upper extremities, the small pulse pressure, the reduced vital capacity, the decreased urinary output and the development of a secondary polycythemia.

Course.—On October 18, 1938, 2 cc. of mercupurin [a mercurin-theophylline preparation] (fig. 1) was given intravenously with a resulting diuresis of 2,000 cc. of urine. On October 22, 7,350 cc. of straw-colored fluid was removed from the peritoneal cavity. The specific gravity of this fluid was 1.013; the cell count was 4,400 with 91 per cent monocytes and 9 per cent polymorphonuclear neutrophils; there were 15 Gm. of protein per liter. No mucin was found. Examinations of the fluid for tumor cells and for tubercle bacilli gave negative results. On October 25, 6,250 cc. of fluid was removed. After the removal of fluid, venous pressure, as recorded in the antecubital vein by the direct method, was 19 cm. of blood (fig. 1). No essential change in the blood pressure was noted. After paracentesis the liver was easily palpable and had a smooth, slightly tender surface. No other

abdominal masses were felt. The ascites rapidly reaccumulated. Studies were carried out to determine if there was any hepatic dysfunction. There was 30 per cent retention of bromsulphalein at the end of thirty minutes. The twenty-four hour specimen of urine contained 13 mg. of urobilinogen (the upper limit of normal being 3.5 mg. per day). The Takata-Ara test gave positive results, precipitation occurring in tubes 1, 2, 3, 4, 5 and 6. The levulose tolerance test gave positive results, the combined two hour rise being 134.

On October 23 fluoroscopic examination of the heart was carried out to determine whether the patient had constrictive pericarditis. No cardiac enlargement was noted, and all chambers showed good pulsations. There was no fixation of the heart. On October 26 kymographic studies showed fair amplitude of all cardiac pulsations. From these studies it was apparent that the patient did not have constrictive pericarditis. On October 31 it was noted that the superficial veins of the abdomen and of the lower portion of the chest were becoming more prominent. One of the collateral veins on the right side of the abdomen became thrombosed. The direction of the blood flow in the superficial veins of the abdomen was noted to be upward.

On October 28 the hemoglobin content had risen to 108 per cent. The red cell count was 5,750,000. The sedimentation rate showed no fall in the red blood cell count in the first hour and a fall of 2 mm. in the second hour. Rapid accumulation of the ascites continued; hence, on November 6 it was again necessary to perform paracentesis, with a yield of 8,800 cc. of straw-colored fluid. After this procedure the patient went into a state of shock, the pulse became thready and weak, and the blood pressure fell to 70 systolic and 50 diastolic. She recovered quickly from this, however.

On November 11 the venous pressure as estimated in the antecubital vein was found to be 16 cm. of blood, and when pressure was applied over the hepatic region no change in the height of the venous pressure column was noted (fig. 1). This obviously indicated that there was an obstruction to the outflow of blood from the liver into the inferior vena cava. Mercupurin was given at this time with only fair results.

Reexamination with the kymogram during phases of inspiration and expiration showed a typical paradoxic pulse. On expiration, however, there was good pulsation of both left and right sides of the heart, especially the left. The appearance was not at all suggestive of constrictive pericarditis. Marked pulsation of the diaphragm synchronous with that of the heart was present, especially on the right side. This could have indicated the presence of deep-seated diaphragmatic adhesions. The conclusion was that on the left side of the heart there were no adhesions of the pericardium. On the right side, however, some adhesions could have been present, but they were not demonstrable.

On November 15 the polycythemia had become more marked. At this time the hemoglobin content was 114 per cent and the red blood cell count 6,750,000, with 15,000 leukocytes. The hematocrit reading was 38.3 per cent. On this day the venous pressure in the antecubital vein was measured again and observed to be at the level previously noted (fig. 1). Pressure on the liver again failed to influence the venous pressure. On November 19 paracentesis was carried out and 6,500 cc. of reddish turbid fluid removed. Later in the same day the patient's condition became much worse, with appearance of extreme dyspnea and moderate cyanosis. The skin became cold, and the blood pressure was recorded at 98 systolic and 90 diastolic. The latter measurement was confirmed. The patient was placed in an oxygen tent, and external heat was applied. This treatment did not improve her condition. By the evening of November 19 the patient was in a moribund state.

The blood pressure could not be recorded. The pulse was irregular and thready. The respiratory rate dropped to 4, and breathing became extremely labored. The patient died shortly thereafter.

The outstanding features in the history were progressive weakness and dyspnea, attacks of nausea and vomiting, rapidly appearing edema of the lower extremities and abdominal distention for about four weeks prior to the patient's admission to the hospital. The pertinent clinical features were marked ascites, edema of the lower extremities extending up to the thighs, paradoxic pulse, small pulse pressure, enlarged liver and increased venous pressure in the upper extremities. The course of the disease was characterized by rapidly reaccumulating ascites. The total duration of the disease from the onset of obstructive symptoms to death was approximately twelve weeks. No doubt the tumor had been present for a considerable length of time before the onset of the symptoms, for the microscopic examination revealed a slow-growing tumor of low grade malignancy. The onset of the symptoms corresponded in all probability to that stage of obliteration of the inferior vena cava where the return flow of blood to the right auricle was being seriously impeded.

Pathologic Observations.—Necropsy was performed by Dr. Berman eight hours after death. The body was that of a well developed and well nourished white woman; it measured 169 cm. in length and weighed about 145 pounds (65.8 Kg.). Jaundice was absent. There were severe posterior hypostasis, slight cyanosis of the nailbeds and marked pitting edema of both lower extremities to the level of the inguinal ligaments. The subcutaneous veins of the lower half of the thorax and the upper portion of the abdomen were apparent.

The peritoneal cavity contained 100 cc. of clear amber fluid. Numerous capillaries and small vessels transversed the entire parietal peritoneum. The edge of the liver was 13 cm. below the right costal margin in the midclavicular line. The diaphragm reached to the fourth rib on the right and the fifth rib on the left.

The right pleural cavity contained 1,200 cc. of opalescent amber fluid; the left was dry. There were no adhesions or scars on the surfaces of either lung. The pericardial sac was normal.

The heart weighed 260 Gm. There was no apparent hypertrophy or dilatation of any of the chambers and no lesions or deformities of the valves, septums or myocardium. There were no anomalies of the vessels of the neck or mediastinum. The coronary arteries were free of change. The superior vena cava and the right atrium were distended with blood, but there were no constrictions about any of the great vessels of the heart.

The inferior vena cava was obstructed by a tumor arising in the wall of the vessel. The tumor was 5 by 10 by 5 cm. (fig. 2). Its upper pole lay at a point a few millimeters inferior to the valve of the vena cava; its lower pole was 10 cm. inferior to the valve of the vena cava, and there was a blunt extension of the mass into the right hepatic vein for a distance of 4 cm. The lumen of the inferior vena cava below the mass was 3 mm. in diameter in the narrowest part because of the presence of thrombus, which extended down the vena cava into both common iliac veins. The thrombus extended into the left renal vein for 1 cm., but the renal vein was not completely occluded. The right ovarian vein contained canalized thrombus. The right renal vein and the left ovarian vein contained only fluid blood. A number of small veins in the broad ligament contained thrombi.

The spleen weighed 150 Gm. Trabeculae and corpuscles were apparent. There were no lesions in the esophagus, stomach, small intestine, appendix or colon. The pancreas, adrenal glands, kidneys, bladder and genitalia were normal grossly.

On the upper surface of the right lobe of the liver there was a slightly depressed dark red area connected by a narrow isthmus to a similar area in the lower third of the right lobe. On section, this was observed to be the external surface of deeply congested hepatic substance occupying the lateral half of the right lobe of the liver. The remainder of the liver was less severely congested. There were no lesions of the gallbladder or of the bilary ducts.

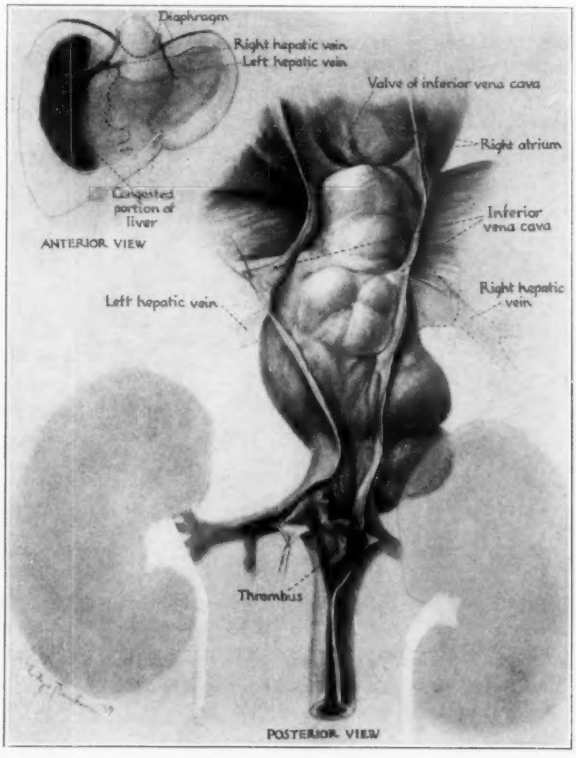

Fig. 2.—Drawing of the tumor (leiomyosarcoma) showing its origin and the extent of involvement of the inferior vena cava. The drawing in the upper left hand corner shows the extension of the tumor mass for a short distance into the right hepatic vein. As a result only the right lobe of the liver was severely congested.

The tumor in the inferior vena cava had a generally smooth surface grooved with many furrows, which divided the mass into a number of rounded elevations. The tissue had an opaque white color and a rubbery consistence. The wall of the inferior vena cava could be reflected from it with ease, except where it was attached laterally to the right side of the tumor. The vessel was thin, and it was applied

closely to the contours of the tumor. In a few places it was slightly adherent. There was a narrow slitlike passage between the tumor and the wall of the hepatic vein from the left lobe of the liver.

On section of the tumor there were seen numerous irregularly arranged filaments and whorls of tissue. The entire mass was solid and elastic, without any gross evidence of degeneration.

Microscopic sections revealed the tumor to consist of a network of spindle-shaped cells in longitudinal section enclosing bundles of cells in cross section. The cell bodies were long, some measuring 150 microns. Their cytoplasm was acidophilic and abundant, and their nuclei were long and rod shaped, with blunt rounded ends. The cells were generally uniform in size, except in the parts of the tumor showing more rapid and irregular growth. In such parts there were numerous cells with large and irregular, and sometimes multiple nuclei, some of

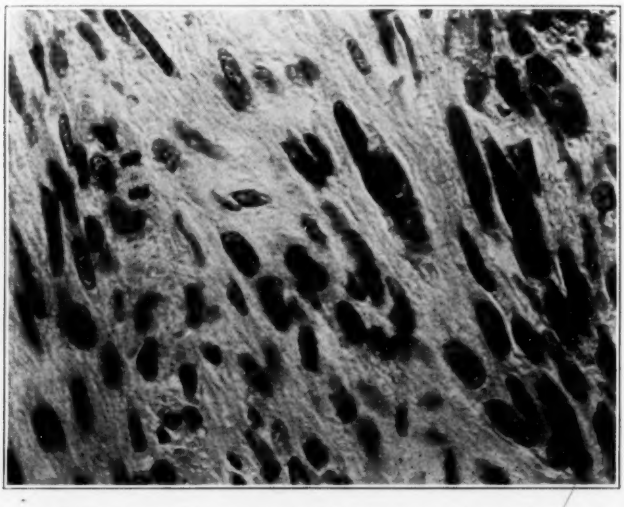

Fig. 3.—Photomicrograph of a section of the tumor of the inferior vena cava (leiomyosarcoma); × 560. Note the abundant cytoplasm and the rod-shaped nuclei. A mitotic figure is present in the upper left corner.

which were undergoing mitosis (fig. 3). Occasional areas of hyaline degeneration were encountered. The presence of collagenous fibrils between the cells was demonstrated by the use of connective tissue stains.

The morphologic structure of the cells and the architecture of the tumor were characteristic of smooth muscle cell tumors, and the occasional parts showing rapid and irregular growth revealed the sarcomatous character of the tumor. Therefore we considered it to be a leiomyosarcoma of low grade malignancy.

Sections from the liver revealed severe chronic passive congestion in the lateral half of the right lobe and less severe passive congestion of the remainder of the liver. The other viscera showed no significant histologic changes.

REVIEW OF THE LITERATURE

Perl [1] in 1871 reported the first case of primary tumor of the vena cava inferior. The patient was a 34 year old woman who complained of pain in the sacral region and lower part of the abdomen for nine months. Signs of obstruction appeared about six weeks before death. Edema of the ankles appeared, progressed and rapidly extended upward to the trunk. Dilated superficial veins appeared on the abdomen and thorax. Ascites developed, and a ballotable mass was present in the right upper quadrant. Because of the presence of casts in the urine and the development of oliguria, a diagnosis of chronic nephritis was made. Autopsy revealed marked ascites, and a retroperitoneal tumor was observed to arise in the inferior vena cava, expanding it to about the size of a fist. The tumor was located at a point just below the hepatic veins and extended into the renal veins. On the basis of the microscopic picture, Virchow made a diagnosis of myosarcoma.

The second case was reported by Unruh [2] in 1896. The patient was a 1 year old child with edema of the legs, which quickly progressed. There were no ascites; albuminuria and oliguria were observed. Rapid enlargement of the liver down to the midabdomen was noted. Jaundice did not appear. The veins of the lateral portions of the abdomen became noticeable, and anasarca developed. The pulse was rapid. Because of dyspnea and signs of compression of the left lung and widening of the cardiac borders, a diagnosis of pericardial effusion was made. The duration of symptoms of caval obstruction was about six weeks. Autopsy revealed enormous edema of the lower extremities, and 100 cc. of ascitic fluid and 300 cc. of pericardial fluid were found. The heart itself was normal. A hard white nodular tumor was found to occupy the inferior vena cava, extending from the hepatic veins for several centimeters into the right auricle. The hepatic veins were filled with thrombi, as was the portion of the inferior vena cava below the tumor. The portal vein was normal. Microscopic examination of the tumor revealed it to be endothelioma.

The third case was reported by Melchior [3] in 1928. The patient was a woman 24 years of age. The chief complaints were of intermittent pain in the sacral region for two years. She was treated for sciatica. Later she complained of a sense of fulness in the abdomen, accompanied

1. Perl, L.: Ein Fall von Sarkom der Vena cava inferior, Virchows Arch. f. path. Anat. **53**:378, 1871.

2. Unruh, F.: In vivo diagnosticirte Thrombose der Vena cava inferior verursacht durch ein Endotheliom der Wand bei einen einjährigen Kinde, Deutsche med. Wchnschr. **22**:746, 1896.

3. Melchior, E.: Sarkom der Vena cava inferior, Deutsche Ztschr. f. Chir. **213**:135, 1928.

by occasional vomiting. A tumor as large as a fist was palpable in the right upper quadrant. The colon appeared to lie over this mass. A diagnosis of an inflammatory cyst of the pancreas was first considered, and an exploratory operation was done. A tumor was removed which was observed to be a portion of the inferior vena cava. The diagnosis of the specimen was fibrosarcoma of the inferior vena cava. The patient died subsequently of gangrene of the lung. Permission for autopsy was not obtained.

The fourth case was reported by König [4] in 1931, the patient being a 29 year old woman. In 1929 a sarcoma of the ovary was removed. In 1930 a distinct mass appeared in the right upper quadrant. The tumor was nontender, lay deep in the abdomen and was diagnosed as a retroperitoneal sarcoma. An exploratory operation was performed, and a tumor 6 cm. long, well encapsulated and occupying the inferior vena cava was removed. Microscopic examination showed it to be a round cell sarcoma. Ten months after the operation the patient was still in excellent condition. However, whether the tumor removed from the inferior vena cava was primary or secondary to the ovarian sarcoma was not definitely determined.

DIFFERENTIAL DIAGNOSIS AND PATHOLOGIC PHYSIOLOGY

Constrictive Pericarditis.—From a consideration of the clinical and the laboratory data in the case reported here, various diagnostic possibilities were considered. As previously stated, constrictive pericarditis appeared at first sight as the most logical diagnosis. This was suggested by rapidly recurring ascites, paradoxic pulse, small pulse pressure, increased venous pressure in the upper extremities and edema of the lower extremities. The electrocardiographic changes of low voltage also supported this view. The diagnosis, however, had to be discarded when fluoroscopic examination of the heart revealed normal pulsation of all chambers, a feature which is invariably absent in chronic cardiac compression due to pericardial disease. The kymographic studies showing the normal amplitude of pulsations of all chambers and great vessels of the heart substantiated the absence of any constrictive phenomena.

Portal Cirrhosis.—Because of definite evidence of dysfunction of the liver as indicated by hepatic function tests, a diagnosis of portal cirrhosis was considered. However, features of cirrhosis, such as nodular liver, jaundice, splenomegaly, macrocytic anemia and spider angiomas, were not present. The large smooth liver and the presence of urobilinogenuria were explained more readily on the basis of chronic passive congestion. This was likewise thought to explain the transitory albuminuria.

4. König, E.: Sarkome der Vena cava inferior, Chirurg **3**:104, 1931.

Furthermore, the vascular signs noted in this case have not been described in cases of cirrhosis of the liver.

Chiari's Disease.—Obliterating endophlebitis of the hepatic veins, Chiari's disease,[5] has similar features in many respects to those in the present case. Chiari's disease, so far as can be determined, has never been diagnosed during life, being usually mistaken for cirrhosis of the liver. Briefly, the clinical picture [6] is one of gradual onset over a period of several months, with the development of marked ascites which accumulates rapidly after removal. The liver is enlarged. The spleen may be enlarged, and there may be slight jaundice. Albuminuria has been noted at times and probably indicates secondary obstruction of the vena cava. Gastrointestinal symptoms are marked, and a superficial collateral circulation indistinguishable from that seen in cirrhosis is present.

Thrombosis of the hepatic veins may occur as a rare complication of polycythaemia vera.[7] However, the fact that the signs of polycythemia were not present at the onset of the disease ruled against a diagnosis of polycythaemia vera in our case. The polycythemia which gradually appeared was in all probability due to hemoconcentration above the diaphragm. Had studies been carried out on blood removed from a vein of the lower extremity, it might have been possible to clarify this question.

There are many other causes of obliteration of the vena cava inferior which must be considered in a differential diagnosis, such as thrombosis arising in the vena cava itself as a result of infectious diseases or by extension from localized foci of diseases, as in puerperal sepsis or diseases of the liver. Obstruction of the vena cava may be caused by new growths which may either invade the vena cava or cause external pressure from without, such as tumors, gummas, enlarged peritoneal glands, pancreatic cysts or hepatic abscesses. Congenital obliteration of the vena cava inferior is also a rare possibility.

While it may be often impossible to determine the etiologic factor which is responsible for caval obstruction, it may be possible to determine the level at which the obstruction occurs. For the purpose of differential diagnosis the vena cava may be divided roughly into three anatomic divisions: the upper third, that portion of the vena cava which extends from the entrance of the hepatic veins to the right auricle (sub-

5. Chiari, H.: Ueber die seltständige Endophlebitis obliterans der Haupstämme der Venae hepaticae als Todesursache, Beitr. z. path. Anat. u. z. allg. Path. **26:** 1, 1899.

6. Eppinger, H.: Die Leberkrankheiten, Berlin, Julius Springer, 1937, p. 469.

7. Sohval, A. R.: Hepatic Complications in Polycythaemia Vera, Arch. Int. Med. **62:**925 (Dec.) 1938.

diaphragmatic portion); the middle third, that section extending from below the opening of the hepatic veins to the renal veins, and the lower third, that section extending from below the entrance of the renal veins to the bifurcation into the common iliac veins.

The following physical features are listed according to the level of obstruction:

1. Lower Third
   (*a*) Absence of edema of lower extremities, unless involvement of either one or both common iliac veins is present
   (*b*) Superficial collateral circulation, manifested by development of superficial veins in groins and over lower part of abdomen and flanks
   (*c*) Absence of albuminuria
2. Middle Third
   (*a*) Edema of lower extremities, followed by development of a superficial collateral circulation (occurs in practically all cases of gradual occlusion)
   (*b*) Albuminuria as a rule
   (*c*) Occasional presence of edema of abdominal wall
3. Upper Third (subdiaphragmatic obstruction)
   (*a*) Ascites
   (*b*) Edema of lower extremities
   (*c*) Enlargement of liver
   (*d*) Albuminuria
   (*e*) Development of superficial collateral circulation

The following signs are added to high caval obstruction from the observations made in the study of this case:

(*f*) Paradoxic pulse
(*g*) Low pulse pressure
(*h*) Electrocardiographic changes
(*i*) Increased venous pressure in upper extremities and failure to raise venous pressure in upper extremities when pressure is applied over liver

An exceptional feature was the presence of increased venous pressure in the upper extremities (fig. 1). While no measurements of venous pressure could be made in the lower extremities because of the massive edema, it was reasonable to assume that the venous pressure was abnormally elevated and that this increased pressure was transmitted upward along the collateral circulation to the tributaries of the superior vena cava. Hence, it would appear that the return of an abnormal volume of blood to the heart through the superior vena cava by way of the collateral circulation could have produced a certain amount of engorgement of some of the principal veins emptying into it. Presumably this engorgement would be reflected as increased venous pressure in the antecubital veins, the point at which the venous pressure determinations were made.

This is not at all impossible to comprehend when it is remembered that the superior vena cava is normally adapted to carry only about a third of the venous blood returned to the right atrium. With closure of the inferior vena cava this quantity is much increased, and from the

point of view of dynamics it seems likely that the superior vena cava cannot carry the larger amounts of blood without elevation of pressure in the tributary veins.

The paradoxic pulse was one of the most striking features in this case, and its presence strongly suggested the diagnosis of compression of the heart. As yet the mechanism of the production of the intrinsic variety of paradoxic pulse has not been elucidated clearly, although many theories have been advanced for its explanation. However, certain conditions must operate to bring it about. There must occur a marked reduction at the end of inspiration in the stroke output of the heart which is responsible for a diminution in the amplitude of the radial pulse. The reduced stroke output is a consequence of the failure of the right or left auricle to fill adequately during the inspiratory phase. We can only speculate as to the mechanism that produced the paradoxic pulse in this case. It is believed that the chief collateral circulation from the inferior vena cava occurred by way of the lumbar veins to the ascending lumbar veins, which in turn drained into the azygos vein and thence into the superior vena cava. Anatomically, the azygos vein at its termination arches over the root of the right lung before it makes its entrance into the superior vena cava. Thus it lies in direct proximity to the medial surface of the right lung. If we assume that the azygos vein is abnormally dilated because of increased blood flow through it, then on deep inspiration the pressure exerted on its wall by the inflating lung would tend to compress it so as to cut down the flow of blood into the superior vena cava. Obviously the downward expansion of the lung in the present case was limited by the high diaphragm, and the greatest expansion would occur in a transverse direction. On deflation of the lungs, compression of the azygos vein would tend to be removed.

The electrocardiographic changes are best explained by a reduced flow of blood into the heart, the coronary flow being simultaneously reduced; thus a state of coronary insufficiency develops similar to the condition that obtains in constrictive pericarditis.

SUMMARY

A case of occlusion of the subdiaphragmatic portion of the inferior vena cava by a leiomyosarcoma is reported. The literature of occlusion of the vena cava inferior by primary tumors is reviewed.

The presence of paradoxic pulse and of high venous pressure in the upper extremities were clinical features which complicated the differential diagnosis. The possible mechanisms by which these phenomena were produced are discussed.

Similarity to Chiari's disease, obliterating endophlebitis of the hepatic veins, was noted in the present case. Clinical features are discussed which may serve to distinguish the two conditions in the future.

DIAGNOSTIC SIGNIFICANCE OF DETERMINATIONS OF SERUM LIPASE

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A review of recent experimental and clinical data suggests that determinations of serum lipase may be of value in the diagnosis of diseases of the pancreas. The reports in the literature are limited largely to application of the test to groups of selected patients with pancreatic and hepatic diseases. This report is concerned with an analysis of the results of this test on a wide variety of clinical material over a period of three years. It was thought that this type of study might throw some light on the degree of specificity of the test for pancreatic disease and might possibly help to clarify the relation between hepatic dysfunction and hyperlipasemia.

METHOD

We used a modification of the Loevenhart method, as suggested by Cherry and Crandall.[1] Basically, the method depends on the estimation of fatty acid produced by the hydrolysis of an olive oil emulsion on which the lipase in the blood serum has been acting during a twenty-four hour period under optimum conditions of p_H and temperature. The determination of serum lipase is carried out in the following manner:

1. Place 3 cc. of distilled water in each of two test tubes, *A* and *B*.
2. Add 1 cc. of serum to each tube and shake.
3. Place tube *A* in a water bath at 100 C. for five minutes to inactivate the lipase. Tube *A* is the control tube. Be sure to cool tube *A* before proceeding to step 4.
4. Add 0.5 cc. of buffer solution to each tube. (Prepare the solution as follows: Mix 10 cc. of a one-third molar solution of disodium hydrogen phosphate [Na_2HPO_4] and 3 cc. of a one-third molar solution of potassium dihydrogen phosphate [KH_2PO_4].)
5. Add 2 cc. of a 50 per cent olive oil emulsion to each tube and shake. (The substrate was prepared by the Abbott Laboratories, list 8100, with 5 per

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1. Cherry, I. S., and Crandall, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury, Am. J. Physiol. **100**:266 (April) 1932. In the interpretation of studies of serum lipase reported prior to 1932, it is essential to determine what substrate was employed. At that time Cherry and Crandall showed that true lipase, which splits olive oil, differs from esterase, which acts on simple esters such as ethyl butyrate or tributyrin.

cent solution of acacia, as the emulsifying agent, to which 0.2 per cent of sodium benzoate had been added as a preservative.)

6. Incubate for twenty-four hours at 37.5 C.

7. Add 3 cc. of 95 per cent alcohol and 2 drops of a 1 per cent solution of phenolphthalein.

8. Titrate each tube to a faint pink, using a twentieth-normal solution of sodium hydroxide.

9. Subtract the value for control *A* from that for specimen *B*.

10. Results are thus expressed in terms of cubic centimeters of a twentieth-normal solution of sodium hydroxide.

Previous observers have not agreed on a figure for serum lipase which can be accepted as the upper limit of normal. From the point of view of quantitative chemistry, the test is somewhat short of the ideal. Different batches of olive oil emulsion show slight variations in the amount of titratable acidity in the control specimens, probably referable to varying amounts of free fatty acids in the substrate. It is possible that different batches of olive oil emulsion may vary as to the ease with which the olive oil may be broken down by the serum lipase. The composition of an olive oil emulsion at different periods after its preparation offers a variable which is difficult to evaluate. An attempt to measure accurately 2 cc. of a heavy olive oil emulsion offers in itself a sizeable variant in individual instances. However, values for duplicate determinations on the same specimens, particularly those of higher lipase content, have been surprisingly close.

Comfort [2] stated that significant values are in excess of 1.5 cc. of twentieth-normal solution of sodium hydroxide. An analysis of our preliminary determinations indicated that some importance might be attached to any figure above 1.0 cc. Temporarily, for our series, we are accepting the latter figure as the maximum normal. However, the most significant figures occur in the higher brackets. Our highest value, 5.5 cc., is somewhat lower than the highest value reported by Comfort.[3] We are unable to account for our inability to obtain by titration values in excess of approximately 5.0 cc. in cases of acute pancreatitis. However, for experimentally induced acute pancreatitis in dogs Baxter, Baxter and McIntosh [4] reported values ranging from 3.0 to 5.5 cc., values not dissimilar to our maximum figures for acute pancreatitis.

The serum lipase is said to be maintained at normal levels for at least two weeks after operation in pancreatectomized dogs, from which

2. Comfort, M.: Serum Lipase: Its Diagnostic Value, Proc. Staff Meet., Mayo Clin. **10**:810 (Dec. 18) 1935.

3. Comfort, M.: Serum Lipase: Its Diagnostic Value, Am. J. Digest. Dis. & Nutrition **3**:817 (Jan.) 1937.

4. Baxter, H.; Baxter, S. G., and McIntosh, J. F.: Variations in the Level of Serum Lipase in Experimental Pancreatitis, Am. J. Digest. Dis. & Nutrition **5**:423 (Sept.) 1938.

one would infer that a functioning pancreas is not essential for the maintenance of a normal level. There is some experimental work supporting the theory that the source of the normally circulating serum lipase is not the pancreas but is possibly the liver or muscles, or both. According to that theory, serum lipase of pancreatic origin enters the blood stream only after trauma to the pancreas or after obstruction of the pancreatic ducts. The validity of the hypothesis is not above question (case 400).

ANALYSIS OF VALUES FOR SERUM LIPASE IN 371 CASES

Determinations were carried out in 371 cases during the course of this study, from November 1935 to November 1938. Determinations in approximately 75 additional cases were excluded because of lack of sufficient clinical data. All of the determinations were carried out by one or the other of two persons, to minimize the personal equation in the

TABLE 1.—*Range of Abnormal Serum Lipase Values*

Serum Lipase, in Cc. N/20 NaOH	Number of Determinations
1.01 to 1.50	38
1.51 to 2.00	16
2.01 to 2.50	16
2.51 to 3.00	2
3.01 to 3.50	6
3.51 to 4.00	2
4.01 to 4.50	3
4.51 to 5.00	1
5.01 to 5.50	2
Total	86

interpretation of results. In some instances many tests were performed in the same case during the course of the illness. Six hundred and sixteen separate determinations, not including duplicate tests on the same day, were made during the period. All values in excess of 1.0 cc. were considered abnormal. In 50 cases (13.5 per cent) there were readings above that level. Eighty-six separate determinations (14 per cent) were above 1.0 cc. The number of determinations within the abnormal range may be seen in table 1.

Acute Pancreatitis.—Forty separate determinations of serum lipase were carried out in 11 cases of acute pancreatitis. In 9 cases the values were high at some time during the course of the illness. Normal values were obtained in 2 cases. In case 78 the presence of acute pancreatitis was probable, but the diagnosis was not absolutely established. In case 439 the first lipase determination was made two weeks before the condition was found at operation, and the second test was carried out one week after operation. The case reports follow:

CASE 35.—The value for lipase was 4.0 cc. The diagnosis of acute pancreatitis was made clinically; recovery took place without operation.

CASE 51.—Acute hemorrhagic necrosis of the pancreas was found at operation; the pancreas was incised from head to tail. Preoperatively the values for lipase were 2.2 and 0.8 cc. Immediately after operation the value was 3.1 cc., and eight months after recovery it was 0.26 cc.

CASE 78.—The findings at operation were atypical: fatty necrosis of omentum in the region of the pancreas; unidentified necrotic material in the lesser peritoneal sac, and cholelithiasis. Recovery took place. The lipase values were 0.2, 0.5, 0.16, 0.26 and 0.52 cc.

CASE 106.—The lipase value was 2.5 cc. The diagnosis was clinical only; recovery took place without operation.

CASE 131.—G. C., a white man, was admitted to the hospital on Sept. 25, 1937, with jaundice of three weeks' duration and with a history of intermittent attacks of epigastric pain. There was no visualization of the gallbladder by intravenous cholecystography. The value for serum bilirubin was 6 mg. per hundred cubic centimeters. The bromsulphalein retention (dose, 2 mg. per kilogram of body weight) was 60 per cent. The value for serum lipase was 1.2 cc. On October 9 the jaundice had receded (bilirubin, 3 mg.); the bromsulphalein retention was 45 per cent. The lipase values were 0.94 cc. on October 2 and 0.46 cc. on October 9. Exploratory operation on October 10 revealed a sizable soft mass which involved the head of the pancreas. Cholecystostomy was performed. Hyperbilirubinemia and excessive retention of dye were no longer noted. There was a recurrence of pain on November 10 with reopening of the biliary fistula. The value for serum lipase was 0.96 cc. on November 9 and 0.78 cc. on November 16. The fistula was closed; there was an uneventful convalescence to November 24, at which time the patient was discharged. Follow-up study showed lipase values of 2.8 cc. on November 30, 1.8 cc. on December 4 and 0.18 cc. on April 19, 1938. Observation was continued to March 1939, at which time the patient was admitted for standardization for diabetes which had developed apparently as a result of the pancreatic inflammation. The lipase values at the time were 0.8 and 0.42 cc.

CASE 192.—Acute hemorrhagic pancreatitis was found at operation. The lipase value was 1.68 cc. four days after operation; recovery took place.

CASE 302.—A white woman 38 years of age was admitted to the hospital for study on April 2, 1938, because of attacks of biliary colic since her pregnancy in June 1937. The level of serum bilirubin was normal, and the lipase value was 0.74 cc. While under observation the patient had an attack of severe pain in the upper abdominal region, accompanied by slight fever without leukocytosis and followed by jaundice. On April 21, three days after the attack, the value for serum bilirubin was 6 mg. per hundred cubic centimeters and that for lipase was 1.86 cc. The values for lipase on April 24 and on April 25 were 1.38 and 1.34 cc. Operation was deferred until April 25, several days after subsidence of the attack and the jaundice. The gallbladder, filled with stones, was removed. The common duct and the head of the pancreas were thought to be slightly larger than normal but of normal consistency. The duct was not probed. Recovery was uneventful. On May 8 the values for serum bilirubin and for lipase (0.80 cc.) were normal. It is probable that the elevation of the value for lipase had been due to an acute transient pancreatitis.

CASE 400.—A white woman aged 48 was admitted to a colleague's service with acute pain in the upper abdominal region which radiated to the back, nausea, vomiting, a leukocyte count of 20,000, with 84 per cent neutrophils, and a fasting blood sugar of 366 mg. per hundred cubic centimeters. There was no jaundice. After three days the value for serum lipase was 4.18 cc. Death occurred on the

eleventh day, at which time the serum lipase was 0.06 cc. Autopsy revealed a severe hemorrhagic necrosis of practically the entire pancreas. The almost complete disappearance of lipase from the blood stream is of interest in view of the lack of any appreciably functioning pancreatic tissue at necropsy.

CASE 373.—A woman 55 years of age complained of repeated attacks of epigastric pain radiating to the back, of five months' duration. Cholecystectomy had been performed many years previously; there was a recurrence of pain the day before admission on June 7, 1938. The value for serum bilirubin was 4 mg., and the lipase value was 3.32 cc. By June 14 the attack had subsided, and the lipase level was 2.36 cc. Pain recurred on July 1. The next day the lipase level was 5.2 cc., and the serum bilirubin mounted to 2.6 mg. The patient remained symptom free thereafter; an exploratory operation was not done because she had severe myocardial degeneration with auricular fibrillation. The presumptive diagnosis was recurrent subacute pancreatitis, possibly associated with stone in the common duct.

CASE 439.—This patient had cholelithiasis, with slight jaundice. The serum lipase level on admission was 0.04 cc. At operation, two weeks later, areas of pancreatic necrosis were noted, in addition to gallstones. There had been nothing in the clinical course to suggest pancreatitis. Convalescence was uneventful. The lipase value one week after operation was again normal, 0.12 cc.

CASE 444.—A woman 47 years of age was admitted to the hospital on Dec. 31, 1938, in an attack of biliary colic with chills and fever. There was no hyperbilirubinemia, but the sugar tolerance was decreased. On Jan. 2, 1939, the value for serum lipase was 2.34 cc.; on January 4, 1.86 cc.; on January 5, 2.14 cc., and on January 10, 1.18 cc. Operation on January 12 revealed a thickened gallbladder, filled with stones; grossly, the common duct and pancreas appeared to be normal. Cholecystectomy was performed. Lipase values on January 21 and April 2 were 0.90 and 0.40 cc., respectively. We assumed that some inflammation of the pancreas, concomitant with the cholelithiasis, had subsided to a great extent before operation.

Comment.—There is ample clinical and experimental evidence that the amount of lipase in the serum is frequently increased in acute pancreatitis. This increase has been accredited to two possible mechanisms: (1) absorption of lipase directly into the blood stream from necrotic pancreatic tissue and (2) absorption of lipase from the smaller pancreatic ducts which have been blocked by edema secondary to adjacent inflammation. In various studies of serum amylase in acute pancreatitis, Gray [5] and his co-workers stated the belief that increases in the amount of this enzyme did not parallel increases in the severity of the disease. Our series is too small to justify similar comment on serum lipase. Gray [5] and his associates mentioned the occurrence of a transient rise of the level of serum amylase in cases of mild acute pancreatitis, the level returning to normal, in some instances, within a few hours. The possibility of a similar transient rise in lipase may be

5. Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Transient Acute Pancreatitis, Ann. Surg. **108**:1029 (Dec.) 1938. Probstein, J. G.; Wheeler, P. A., and Gray, S. H.: Perforated Peptic Ulcer: Its Differentiation from Acute Pancreatitis by Blood Diastase Determinations, J. Lab. & Clin. Med. **24**:449 (Feb.) 1939.

considered in the interpretation of values obtained several days after the onset of the acute attack.

In experiments with dogs, Cherry and Crandall [1] found a secondary rise in serum lipase after ligation of the pancreatic duct. A similar rise occurred in case 51 after incision of the pancreas. In case 400, in which autopsy demonstrated an almost complete necrosis of the pancreas, there was a drop from an initial level of 4.18 cc., eight days before death, to 0.06 cc., a few hours before death. Such a drop might be explained on the basis of pancreatic exhaustion. It is apparent that acute pancreatic inflammation may not always be associated with an elevation in the serum lipase. Comfort reported an instance of that type, and our case 78 falls into the same group. Nevertheless, it is not possible to scan the figures in our cases of acute pancreatitis without concluding that studies of the enzymes in the serum are of tremendous assistance in the diagnosis of acute inflammation of the pancreas. The determination of serum lipase loses some of its clinical value because of the twenty-four hour incubation period which is necessary for the performance of the test by the technic described. The determination of the serum amylase would seem to be of greater clinical value in the cases of acute pancreatitis because of the rapidity with which that test can be performed, either by the copper-reduction method [6] or by viscometric methods,[7] which require only one hour.

Carcinoma of the Pancreas.—Twenty serum lipase determinations are recorded for 8 cases of carcinoma of the pancreas. Values above 1 cc. were obtained in 5 of them (*62.7* per cent). Only cases in which the diagnosis was confirmed by operation or necropsy were considered. The case reports follow:

CASE 23.—The patient suffered from obstructive jaundice and diabetes. At operation cancer of the head of the pancreas was discovered; cholecystogastrostomy was performed. Two lipase determinations were below 0.2 cc.

CASE 36.—One test for lipase gave a value of 0.9 cc. There was obstructive jaundice; operation confirmed the diagnosis; a cholecystojejunosotomy was done.

CASE 54.—The one lipase value determined was 0.8 cc. The operation confirmed the diagnosis of carcinoma of the head of the pancreas with biliary obstruction. The patient died; no necropsy was performed.

6. Somogyi, M.: Studies on Blood Diastase, Proc. Soc. Exper. Biol. & Med. **29**:1126 (June) 1932.

7. Davison, W. C.: Viscometric Method for Quantitative Determination of Amylase, Bull. Johns Hopkins Hosp. **37**:281, 1925. Elman, R.; Arneson, N., and Graham, E. A.: Value of Blood Amylase Estimation in Diagnosis of Pancreatic Disease, Arch. Surg. **19**:943 (Dec.) 1929. Elman, R., and McCaughan, J. M.: Quantitative Determination of Blood Amylase with Viscosimeter, Arch. Int. Med. **40**:58 (July) 1927. McCaughan, J. M.: Value of Estimations of Blood Amylase in the Diagnosis of Suspected Pancreatic Disease, Surg., Gynec. & Obst. **59**:598 (Oct.) 1934.

CASE 56.—Values for lipase were 0.2 and 1.4 cc. Necropsy revealed a carcinoma involving the pancreas, duodenum and ampulla of Vater, with obstruction of the common duct.

CASE 96.—Two tests for lipase gave values of 1.3 and 1.1 cc. Carcinoma of the head of the pancreas, with jaundice, was present. Cholecystojejunostomy was done; autopsy was performed.

CASE 97.—Values obtained in three tests for lipase were as follows: 0.6, 1.1 and 0.1 cc. Carcinoma of the pancreas was present. Cholecystojejunostomy was done.

CASE 259.—The following values were obtained in ten tests for lipase: 5.04, 4.8, 4.2, 4.2, 3.8, 3.5, 2.4, 2.1, 1.9 and 0.48 cc. The patient was jaundiced. There was surgical confirmation of the diagnosis of carcinoma of the head of the pancreas. Cholecystojejunostomy was performed. The progressive drop in values for lipase, which occurred over a period of eleven weeks, is noteworthy. The first two tests were done preoperatively and the last test was done shortly before the patient's death.

CASE 453.—Two tests gave values for lipase of 2.2 and 1.72 cc. At the first operation the condition was thought to be acute pancreatitis, but subsequent operation showed a nodular malignant growth in the pancreas.

Comment.—Carcinoma of the pancreas gave rise to increased values for serum lipase in 62.7 per cent of our cases. The mechanism of the rise is probably best explained on the basis of obstruction to the pancreatic duct. It would seem that as more and more of the pancreatic tissue is replaced by cancerous tissue one may anticipate a concomitant decrease in the serum lipase. In case 259 this mechanism is illustrated. Life was prolonged by cholecystojejunostomy, which relieved the initial jaundice. A progressive decrease in lipase followed. This occurred so quickly during a period of eleven weeks that another explanation suggests itself, namely, that the cholecystojejunostomy caused a subsidence of edema and hence, possibly, a partial release of the pancreatic obstruction. Knowledge of the level of the serum lipase is of no assistance in the differentiation between pancreatitis and carcinoma, although somewhat higher values were present in our cases of acute pancreatitis and in those reported by Comfort.[8] Nor is an elevated serum lipase of great diagnostic assistance in chronic obstructive jaundice. However, in this study carcinoma gave rise to an increase in lipase twice as often as did obstructive jaundice due to gallstones.

Jaundice.—Data for serum lipase in various types of jaundice are given in table 2. Loeper and Soulié[9] have expressed the belief that an inflammatory swelling of the head of the pancreas may accompany catarrhal jaundice. Crandall[10] stated that while an increase in serum

8. Comfort, M., and Osterberg, A. E.: Lipase and Esterase in the Blood Serum, J. Lab. & Clin. Med. **20**:271 (Dec.) 1934.

9. Loeper, M., and Soulié, P.: La participation du pancréas au syndrome d'ictère catarrhal, Nutrition **6**:271, 1936.

10. Crandall, L. A.: Origin and Significance of the Blood Serum Enzymes, Am. J. Digest. Dis. & Nutrition **2**:230 (June) 1935.

lipase may accompany experimental hepatic injury no definite hypothesis has been offered to explain the mechanics of the increase. Our experience with patients, many of whom undoubtedly had some degree of hepatocellular injury, affords no support for the observations of Loeper and Soulié and of Crandall. Thirty serum lipase determinations in 15 cases of so-called catarrhal jaundice failed to show an elevated lipase value in a single instance at any time during the course of the disease. Likewise, although hyperthyroidism is frequently associated with evidence of hepatic dysfunction, the values for serum lipase were

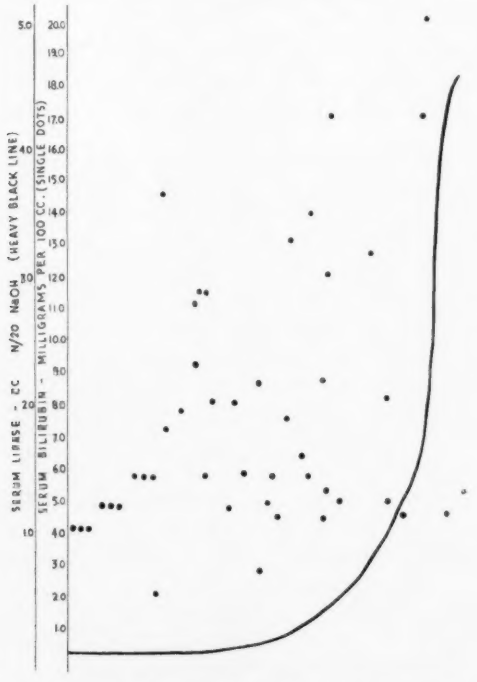
TABLE 2.—*Data on Serum Lipase in Cases of Jaundice*

Diagnosis	No. of Cases	No. of Tests	No. of Cases with Values Below 1 Cc.	No. of Cases with Values Above 1 Cc.	Comment
Catarrhal jaundice.....	15	30	15	0	
Arsenical jaundice.....	1	6	1	0	
Chronic cholangitis....	1	8	1	0	
Hepatitis with pneumonia	1	1	1	0	
Carcinoma of the hepatic ducts	4	5	3	0	
Pericholecystitis.....	2	2	2	0	
Obstructive jaundice of undetermined origin	3	4	2	1	Case 28: Lipase, 0.8 cc.; clinical diagnosis, carcinoma of head of pancreas; no operation or necropsy. Case 55: Lipase, 1.2 cc.; clinical diagnosis, carcinoma of head of pancreas, with diabetes and with metastasis to brain; no operation or necropsy. Case 391: Lipase, 0.30 and 0.10 cc.; clinical diagnosis, carcinoma of head of pancreas; no operation or necropsy
Cancer of ampulla of Vater	1	1	1	0	Case 398: Lipase, 0.48 cc.; cancer of ampulla of Vater, questionable involvement of head of pancreas; cholecystenterostomy; death; no necropsy
Hyperbilirubinemia (latent icterus)	6	9	5	1	Case 250: Lipase, 1.12 and 9.36 cc.; no cause found for hyperbilirubinemia; gallbladder, liver and blood normal

normal in 12 cases of hyperthyroidism in this series (table 5). In 1 case of arsenical hepatitis and in 1 of hepatitis associated with pneumonia there was likewise no elevation in serum lipase. This clinical study supplies no evidence that hepatocellular injury by itself causes an elevation of serum lipase.

If our observations in catarrhal jaundice can be substantiated in a larger series, the test for lipase will be of distinct value in obscure cases of jaundice. An elevated value for lipase possibly can be looked on as militating against a diagnosis of so-called catarrhal jaundice. We are unaware of any previous reference to the use of the test for serum lipase in cases of catarrhal jaundice.

Hyperbilirubinemia and Serum Lipase.—We have not encountered any previous report attempting to determine the relation between hyperbilirubinemia and the content of lipase in the blood. In view of the feeling in some quarters that there is a possible connection between hepatocellular function and the amount of circulating lipase, it was decided to determine the effect of hyperbilirubinemia on the degree of lipasemia. We felt that this relation was deserving of investigation in view of the frequency with which, in certain clinical entities, patients



The values for forty-six determinations of serum lipase were plotted against those for a similar number of determinations of elevated serum bilirubin. In each instance both determinations were run on the same day. There is no constant correlation between the values for serum lipase and for elevated serum bilirubin.

with hyperlipasemia also had jaundice. In the accompanying chart 44 determinations of serum bilirubin for jaundiced patients were plotted against a similar number of determinations of serum lipase. In each instance both determinations were done on the same specimen of blood. It seems obvious that there is no consistent correlation between the two values. Six cases of hyperbilirubinemia without clinical jaundice and

without obvious cause for the increase in bilirubin were also studied (table 2). There was no ascertainable evidence of hepatic dysfunction or of gallbladder disease. In only 1 case of this group was there a slight elevation of lipase above the normal level, and that occurred on only one occasion. Similarly, in 4 cases of carcinoma of the hepatic ducts with complete obstructive jaundice (table 2) there was no increase in serum lipase, a further proof of the lack of influence of jaundice on the content of lipase in the blood.

TABLE 3.—*Data on Serum Lipase in Cases of Disease of the Gallbladder*

Diagnosis	No. of Cases	No. of Tests	No. of Cases with Values Below 1 Cc.	No. of Cases with Values Above 1 Cc.	Comment
Cholelithiasis (a) no jaundice; no history of jaundice; no hyperbilirubinemia	31	35	30	1	Case 386: Lipase, 1.4 and 0.48 cc.; possible subacute transient pancreatitis
(b) With jaundice, history of jaundice or hyperbilirubinemia	29	61	20	9	Case 50: Lipase, 3.30, 0.80 and 0.18 cc.; first test prior to drainage of common duct. Case 69: Lipase, 0.70 and 21 cc.; associated Hodgkin's disease. Case 93: Lipase, 2 and 0.6 cc.; recurrent attacks suggesting stone in common duct. Case 154: Lipase, 1.30, 1.24 and 0.88 cc.; associated pericholecystitis. Case 165: Lipase, 0.72 and 1.92 cc. Case 170: Lipase, 0.72, 1.06 and 0.74 cc. Case 297: Lipase, 2.04 cc. Case 362: Lipase, 0.74, 1.80, 1.38, 1.34 and 0.84 cc.; associated acute pancreatitis. Case 375: Lipase, 2.06 and 2.80 cc.; complicated by partial intestinal obstruction
Cancer of the gallbladder	5	9	5	0	In 2 of these cases there was jaundice, but autopsy revealed no pancreatic involvement
Acute cholecystitis.....	2	5	1	1	Case 65: See table 7
Chronic cholecystitis with calculi	7	7	7	0	Diagnosis not proved; no operation or autopsy

Diseases of the Gallbladder (table 3).—Lipase determinations were made in 60 proved cases of cholelithiasis. In 31 of these cases the patients were not jaundiced, gave no history of jaundice and had normal serum bilirubin. An elevated serum lipase was noted in only 1 of the 31 cases (3.5 per cent). This low incidence of hyperlipasemia contrasts strikingly with the occurrence of increased values for lipase in 9 (31 per cent) of the remaining 29 cases of cholelithiasis complicated by jaundice at the time of testing or some time previously. We have already pointed out that jaundice or hepatocellular injury of themselves rarely cause an elevation of the serum lipase. It would appear that one can assume safely that hyperlipasemia in cholelithiasis is suggestive of, if not pathognomonic for, an associated pancreatitis. This confirms a common clinical observation that pancreatic involvement is more frequently

encountered in cholelithiasis when the condition is associated with jaundice and with calculus in the common duct. In 5 cases of cancer of the gallbladder (2 of which were associated with jaundice) and in 7 cases of chronic noncalculous cholecystitis there were normal values for lipase. Of 2 cases of acute cholecystitis, there was an elevated serum lipase in 1 case, in which there was also heart disease with decompensation.

TABLE 4.—*Data on Serum Lipase in Cases of Chronic Hepatic Disease*

Diagnosis	No. of Cases	No. of Tests	No. of Cases with Values Below 1 Cc.	No. of Cases with Values Above 1 Cc.	Comment
Portal cirrhosis.....	11	30	7	4	Case 40: Lipase, 1.1, 0.56 and 0.28 cc.; associated diabetes; death; patient not acutely ill at time tests were done. Case 176: Lipase, 13 tests with values ranging from 0.36 to 0.74 cc.; 1 test, 1.24 cc.; syphilitic and cardiac factors; possibly not a true portal cirrhosis. Case 191: Lipase, 1.04 and 0.56 cc.; ascites; bromsulfalein retention 60 per cent; positive Takata test; hypoalbuminemia; clinical recovery for six years. Case 376: Lipase, 0.22, 1.32, 1.6 and 1.74 cc.; typical signs and symptoms
Biliary cirrhosis—obstructive and nonobstructive	9	39	8	1	Case 9: Lipase, 1.05 and 2.06 cc.; obstructive biliary cirrhosis; pancreas grossly normal at autopsy
Cirrhosis with hypercholesterinemia	1	1	1	0	Biliary type of cirrhosis with xanthelasmic deposits in skin
Cirrhosis with heart failure	2	3	1	1	Case 119: Lipase, 1.4 and 0.8 cc.; patient believed to have borderline hepatocellular damage
Hanot's cirrhosis.....	1	1	0	1	Case 228: Lipase, 1.02, 1.42 and 1.4 cc.; woman aged 23 with typical signs and symptoms; jaundice of one year's duration; splenomegaly; no ascites and no obstruction
Hemangioma of the liver	1	4	0	1	Case 167: Lipase, 1.28, 1.34 and 1.01 cc.; pathologic diagnosis from section removed surgically; a fourth test one year later, 0.14 cc.; pancreas not examined
Cancer of the liver (secondary)	1	2	0	1	Case 129: Lipase, 3.46 and 2.18 cc.; hepatic cancer secondary to cancer of the sigmoid flexure; pancreas normal at operation; severe jaundice; no follow-up study

Chronic Hepatic Disease (table 4).—Comfort [3] reported increased values for serum lipase in 13 per cent of his cases of hepatic disease. He stated the belief that the increase resulted either from destruction of the hepatic parenchyma or from associated pancreatitis. Our study throws no additional light on the possible relation of chronic hepatic disease to the serum lipase. Twenty-nine per cent (7 cases) of our 24 cases of cirrhosis of the liver were associated with elevated lipase values. In only 1 of this group of cases with hyperlipasemia was the pancreas inspected and said to be normal. In 2 cases of hepatic tumor the serum lipase was elevated; in 1 the pancreas was reported to have

been of normal shape and consistency at operation. Until a large series of cases of chronic hepatic disease is reported, with values for lipase and with complete protocols of necropsies, we are unwilling to accept the view that the hepatic diseases encountered clinically can be considered a frequent cause of elevations in the serum lipase.

Metabolic and Chronic Granulomatous Diseases (table 5).—These disorders were grouped together in an effort to ascertain whether metabolic disturbances associated with an abnormal level of sugar, fat or protein in the blood showed any tendency to disturb the level of lipase

TABLE 5.—*Data on Serum Lipase in Cases of Metabolic and in Chronic Granulomatous Disease*

Diagnosis	No. of Cases	No. of Tests	No. of Cases with Values Below 1 Cc.	No. of Cases with Values Above 1 Cc.	Comment
Diabetes mellitus	18	26	14	4	Case 27: Lipase, 1.95 and 1.35 cc.; associated chronic gastritis. Case 40: Associated portal cirrhosis (see table 4). Case 55: Lipase, 1.20 cc.; pancreatic cancer not excluded. Case 195: Lipase, 0.62, 1.01 and 0.80 cc.
Carotinemia	1	1	1	0	
Hyperinsulinism	1	1	1	0	Case 143: Pancreatic adenoma at operation; test done in preoperative shock-free period
Xanthomatosis	1	1	1	0	
Hyperthyroidism	12	16	12	0	
Hypothyroidism	16	16	16	0	
Syphilis	27	40	25	2	Case 185: Lipase, 1.42 and 0.28 cc.; associated venereal lymphogranuloma. Case 176: Associated portal cirrhosis (see table 4)
Venereal lymphogranuloma	21	25	19	2	Case 185: See case 185 under syphilis. Case 22: Lipase, 1.2 cc.
Tuberculous peritonitis	2	4	2	0	
Pulmonary tuberculosis	3	3	3	0	

in the serum, in the absence of demonstrable disease of the pancreas. In only 2 (11 per cent) of the cases of uncomplicated diabetes mellitus was there hyperlipasemia. It is probable that this incidence does not exceed that of pancreatitis in patients with diabetes. The preponderance of normal values for lipase in diabetes is of interest because it is known that alteration in fat metabolism [11] often accompanies the fundamental disturbance of carbohydrate metabolism in this disease. Hyperthyroidism has been discussed previously. No instance of increase in the serum lipase was encountered in 16 cases of hypothyroidism, in spite of the associated hyperlipidemia in many instances. A review of this material

11. Mosenthal, H. O.: Pancreatitis and Diabetes, Ann. Int. Med. **11**:1001 (Dec.) 1937. Soskin, S., and Mirsky, I. A.: Medical Treatment of Hyperthyroidism with a High Fat Diet, J. A. M. A. **110**:1337 (April 23) 1938.

suggests that in the absence of pancreatic disease an increase in blood lipids is not associated with an elevation of the serum lipase.

We had the opportunity to study the serum lipase in a large group of cases of venereal lymphogranuloma in which studies of plasma proteins had been carried out by Jones and Rome.[12] The hyperglobulinemia so frequently found in this disease was not accompanied by any elevation of the serum lipase. In only 2 of 21 cases was there a slight rise above the normal value for lipase.

TABLE 6.—*Data on Serum Lipase in Cases of Malignant Disease*

Diagnosis	No. of Cases	No. of Tests	No. of Cases with Values Below 1 Cc.	No. of Cases with Values Above 1 Cc.	Comment
Carcinoma of stomach	13	13	12	1	Case 183: Lipase, 1.32 cc.; autopsy showed the pancreas to be free of carcinomatous infiltration, but adjacent lymph glands were involved
Carcinoma of colon....	8	9	7	1	Case 129: See comment, table 4.
Carcinoma of esophagus or of larynx	2	2	2	0	
Carcinoma of esophagus (partial duodenal obstruction)	1	1	1	0	
Carcinoma of kidney...	1	2	1	0	
Sarcoma of jejunum...	1	1	1	0	
Lymphosarcoma of ileum	1	2	1	0	
Leiomyosarcoma of stomach	1	1	1	0	
Lymphoblastoma (retroperitoneal)	1	1	1	0	
Lymphosarcoma with obstructive jaundice	1	2	0	1	Case 21: Lipase, 3.2 and 0.6 cc.; previously proved lymphosarcoma with mediastinal involvement which had responded to roentgen therapy; later developments, obstructive jaundice and roentgen and clinical evidence of mass in region of head of pancreas, with tremendous widening of duodenal loop; mass and jaundice disappeared after roentgen therapy; first test while jaundiced, second test after recovery
Hodgkin's disease.....	3	4	2	1	Case 69: Lipase, 0.7 and 2.1 cc.; associated cholelithiasis and biliary fistula

In only 2 of 27 cases was syphilis associated with increased serum lipase; in 1 of these venereal lymphogranuloma was also present and in the other hepatic cirrhosis was a complication. In 5 cases of tuberculosis the values were normal. It appears from the study of this group that the presence of uncomplicated diabetes mellitus, disease of the thyroid, syphilis, venereal lymphogranuloma or tuberculosis exerts no influence on the level of lipase in the blood.

12. Jones, C. A., and Rome, H. P.: Serum Proteins, Takata-Ara Reaction, and Liver Function Tests in Lymphogranuloma Venereum, Am. J. Clin. Path. **9**:421 (July) 1939.

Malignant Disease (table 6).—A sufficient number of instances of malignancy (32 cases) has been studied to enable us to conclude that malignant disease exerts no effect on the serum lipase. Apparently the associated cachexia and anemia are not factors that disturb the serum lipase. The 4 increased values (cases 183, 129, 69 and 21) in this group can be attributed, we feel, to disturbances of pancreatic function associated with the malignant disease.

TABLE 7.—*Data on Serum Lipase in Cases of Disease of the Stomach, Intestines and Heart*

Diagnosis	No. of Cases	No. of Tests	No. of Cases with Values Below 1 Cc.	No. of Cases with Values Above 1 Cc.	Comment
Gastric ulcer	4	6	4	0	
Duodenal ulcer	10	11	9	1	Case 211: Lipase, 1.4 cc.; osseous tuberculosis and history suggestive of duodenal ulcer; test taken during ulcer flare-up; pancreatic involvement not ruled out
Gastritis or gastroduodenitis	14	17	13	1	Case 27: Lipase, 1.95 and 1.35 cc.; associated diabetes mellitus
Functional colonopathies	30	31	30	0	
Ulcerative colitis	1	2	1	0	
Acute colitis (nonspecific)	2	2	2	0	
Ileocolitis	1	1	1	0	
Diverticulosis coli	2	2	2	0	
Duodenal diverticulum	2	2	2	0	
Intestinal obstruction					
(a) Inguinal hernia	1	2	0	1	Case 43: Lipase, 1.7 and 0.6 cc.
(b) Ileitis	1	1	0	1	Case 31: Lipase, 1.8 cc.
(c) Gallstones	1	2	0	1	Case 375: Lipase, 2.06 and 2.80 cc.
(d) Adhesions	1	1	0	1	Case 412: Lipase, 1.96 cc.
Heart disease					
Rheumatic					
(a) Decompensated	3	6	2	1	Case 65: Lipase, 1.2, 1.4, 0.4 and 0.68 cc.; heart disease associated with an attack of acute cholecystitis
(b) Compensated	3	3	3	0	
Hypertensive	4	4	4	0	
Other	3	3	3	0	

Diseases of the Stomach and Intestines (table 7).—Elevated values for serum lipase have been reported in some cases of duodenal ulcer by Comfort [3] and by Jergeson and Simonds.[13] In 1 (10 per cent) of our cases of suspected duodenal ulcer the lipase was slightly elevated. In only 1 of 14 cases of gastritis and duodenitis was there a rise in lipase and in that case there was associated diabetes. Four patients with gastric ulcer had normal values.

13. Jergeson, F. H., and Simonds, J. P.: Blood Lipase in Patients with Peptic Ulcer, J. Lab. & Clin. Med. **19**:1054 (July) 1934.

In the cases of nonobstructive lesions and functional disorders of the small and large bowel the serum lipase was uniformly normal. The only positive lipase test in this group of 38 cases was obtained in case 27 in which the condition was associated with diabetes.

Intestinal Obstruction (table 7).—We are unable to explain the rise in serum lipase which was encountered in all of the 4 cases of intestinal obstruction which were studied. If observations on a larger series confirm this finding, the test will have an added diagnostic value. It is possible that distention of the duodenum may interfere with the flow of pancreatic juice or that toxins absorbed from above the obstruction may exert a damaging effect on the pancreas or the liver. A more attractive hypothesis would be that there is continued absorption of the lipolytic ferment above the point of obstruction. It is conceivable that the rapidity with which the rise in lipase occurs and the magnitude of the rise may be proportionate to the nearness of the obstruction to the ampulla of Vater.

Heart Disease (table 7).—The data obtained in 10 cases of various types of heart disease offer further confirmation of the consistent normality of the values for lipase found in conditions not associated with pancreatic dysfunction. The lipase values were normal in all cases except 1, in which there were cardiac decompensation and acute cholecystitis and likely some degree of pancreatic inflammation (case 65).

SUMMARY AND CONCLUSION

This report comprises data on 616 independent determinations of serum lipase for 371 patients, performed over a period of three years. The method is described, and its technical difficulties are discussed. Surprisingly uniform results were obtained. In our experience values for serum lipase are significant when they exceed 1 cc. of a twentieth normal solution of sodium hydroxide.

A large number of patients with functional and organic disorders but with no clinical, surgical or pathologic evidence of pancreatic disease were examined in order to determine the incidence of positive tests in nonpancreatic disorders. Uniformly normal lipase values were obtained in uncomplicated diabetes mellitus, hyperthyroidism, syphilis, tuberculosis, hypothyroidism, venereal lymphogranuloma, nonpancreatic malignant disease, uncomplicated peptic ulcer, gastritis, gastroduodenitis, functional colonopathies, nonobstructive organic diseases of the small and large intestines and heart disease. The significance of normal values for lipase in these conditions is emphasized in order to stress the specificity of the test as an indication of pancreatic disease.

This study confirms the reports of others that diseases of the pancreas show the highest incidence of increased values for serum lipase. In 9 of 11 cases of acute pancreatitis and in 5 of 8 cases of proved cancer of the pancreas pathologic values for lipase were obtained. Further proof that disease of the pancreas is the usual cause of elevations in serum lipase is supplied by the data for a group of 60 cases of cholelithiasis. A positive test was obtained in only 1 of 31 cases without jaundice and without a previous history of jaundice, whereas in 31 per cent of the remaining 29 cases of cholelithiasis with jaundice or with a history of jaundice values above 1.0 cc. were obtained.

This study does not supply any support for the view [14] that hepatocellular injury causes an elevation of the serum lipase. Normal values were obtained in 15 cases of so-called catarrhal jaundice, 2 cases of toxic or infectious hepatitis and 12 cases of hyperthyroidism. These findings tend to throw some doubt on the theory that hepatic dysfunction may disturb the level of the serum lipase. If our findings in cases of catarrhal jaundice are confirmed by others, the lipase test may prove to be of distinct value in certain cases of jaundice of obscure causation, for an elevated value for serum lipase would tend to exclude the diagnosis of catarrhal jaundice.

As might have been anticipated, we noted no relation between hyperbilirubinemia and the values for serum lipase. This statement is based on simultaneous determinations of serum lipase and bilirubin on the same blood samples from 44 jaundiced patients. The fact may be considered additional evidence against the theory of a hepatic causation for hyperlipasemia.

In chronic hepatic disease associated with widespread destruction of the hepatic parenchyma there was a rather high incidence of hyperlipasemia. High values were obtained in 7 of 24 cases of cirrhosis of the liver and in 2 cases of hepatic tumor. An examination of the material in table 4 does not supply very convincing evidence that the possibility of pancreatic involvement was satisfactorily eliminated. The pancreas was examined at autopsy in only 1 case (9) and was reported to be normal.

Four patients with intestinal obstruction had elevated values for serum lipase. We have found no reports of a similar observation in the literature. If the observation is confirmed by others, the serum lipase test will have another clinical application of importance.

We feel that this study justifies the conclusion that the serum lipase determination is of considerable clinical importance and that a wider application is warranted than it now enjoys.

14. Zucker, T. F.; Newburger, P. G., and Berg, B. N.: The Amylase of Serum in Relation to Functional States of the Pancreas, Am. J. Physiol. **102**:209 (Oct.) 1932.

BASAL INSULIN REQUIREMENT IN DIABETES MELLITUS

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Usual methods which control mild diabetes frequently fail when applied to the patient who suffers from a more severe form of the disease. Determinations of dextrose excretion and blood sugar at intervals accurately timed in relation to food and insulin intake usually give sufficiently satisfactory information on which to construct a daily program of diet and insulin. Certain patients are seen, however, who despite such careful determinations cannot be kept in stable equilibrium. The blood sugar of these patients fluctuates widely throughout the day, or they have glycosuria and hyperglycemia sometime during the late hours of the night or early morning. The slow-acting insulins were devised particularly for the purpose of smoothing out these diurnal variations, and both protamine zinc insulin and crystalline insulin have been of great help. Still, many who have written on the subject agree that the "unstable" diabetic patient may continue "unstable," even with a protamine zinc insulin regimen.[1]

The most recent trend in diabetic therapy,[2] however, has been the use of one daily injection of protamine zinc insulin, with or without the addition of regular insulin before breakfast. The guiding feature of satisfactory treatment with protamine zinc insulin, as stated by Tolstoi and Weber,[2a] is "the maintenance of weight, freedom from symptoms and absence of ketone bodies in the urine. Glycosuria is desirable, as it affords protection from reactions." That postprandial glycosuria will

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1. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **59**:329-342 (Feb.) 1937.

2. (*a*) Tolstoi, E., and Weber, F. C.: Protamine Zinc Insulin, a Metabolic Study: Treatment in two Cases of Severe Diabetes by Equally and Unequally Divided Diets, with Comments on Criteria for Treatment, Arch. Int. Med. **64**:91-104 (July) 1939. (*b*) Pollack, H., and Dolger, H.: Advantages of Protamine Zinc Insulin Therapy: Dietary Suggestions and Notes on the Management of Cases, Ann. Int. Med. **12**:2010-2021 (June) 1939.

occur with this schedule in the person with severe diabetes is well recognized. Ricketts [3] stated:

> It is apparent in such cases (severe diabetics) that constant supply of insulin derived from the subcutaneous depot of protamine insulin, although it is able to take care of the endogenous carbohydrate metabolism, needs to be augmented at meal time with extra insulin if the blood sugar is to be kept within normal limits. On the other hand, it is well known that in cases in which the disease is relatively mild the blood sugar can be controlled at all time with protamine insulin alone.

It is our experience that the postprandial glycosuria of patients with severe diabetes receiving one injection of protamine zinc insulin daily does not in any way protect them from severe hypoglycemic reactions between midnight and 4 or 5 a. m., even if the fasting morning blood sugar (at 7 to 8 a. m.) is within normal range (75 to 125 mg. per hundred cubic centimeters). The margin of safety in the patient with severe diabetes who has wide variations in the blood sugar content during the day and night is too small. A little excess food may give rise to a hyperglycemia, suddenly associated with ketosis, as we have noted in several patients entering the diabetic service in coma. Careful inquiry has shown that these patients have had no change in the daily amount of insulin and no infections or febrile illnesses to account for the sudden onset of acidosis. An increase in carbohydrate intake, however, was usually admitted. The failure to take the usual amount of food may quickly cause profound hypoglycemia.

The fundamental problem of the harmfulness or innocuousness of wide diurnal fluctuations of blood sugar associated with marked glycosuria cannot be fully settled at present. It seems reasonable to assume that as finely adjusted a mechanism as the normal control of blood sugar cannot be without significance. However, no experimental work to date has adequately proved or disproved this conception. Until this idea is disproved a normal blood sugar curve should be the goal of diabetic therapy, or, as Ricketts [3] stated, "The blood sugar curve of the normal individual may be regarded as the result of a completely adequate pancreatic response."

The two major problems in insulin therapy for the person with severe diabetes may then be said to be (*a*) control of the fluctuations of blood sugar following ingestion of food and (*b*) prevention of hyperglycemia and glycosuria in the postabsorptive or fasting state. The latter may be defined as the basal insulin requirement, a concept which has arisen from the study of the insulin requirement of depancreatized dogs in the laboratory.[4]

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3. Ricketts, H. T.: Carbohydrate Tolerance After Protamine Zinc Insulin: Its Bearing on the Physiology of Insulin Secretion, J. Clin. Investigation **17**:795-801 (Nov.) 1938.

4. Greeley, P. O.: Basal Insulin Requirement of Depancreatized Dogs, Am. J. Physiol. **120**:345-349 (Oct.) 1937.

Depancreatized dogs require, in addition to quickly available insulin to cover the diet, a small, steady supply of insulin to prevent hyperglycemia during the postabsorptive period. The results of an experiment

TABLE 1.—*Basal Insulin Requirement in Depancreatized Dog (Weight, 7.3 Kg.)*

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Intravenous Injections)
8: 30 a. m.	285	...
8: 45 a. m.	...	2
9: 40 a. m.	148	...
10: 15 a. m.	111	...
10: 45 a. m.	110	...
11: 45 a. m.	144	...
12: 10 p. m.	210	...
12: 30 p. m.	...	0.2
12: 50 p. m.	161	...
1: 15 p. m.	158	...
1: 40 p. m.	...	0.12
1: 45 p. m.	129	....
2: 15 p. m.	134	....
2: 55 p. m.	...	0.12
3: 15 p. m.	161	....
3: 48 p. m.	110	....
3: 51 p. m.	...	0.16
4: 16 p. m.	112	....
4: 46 p. m.	117	....
4: 48 p. m.	...	0.12
5: 16 p. m.	100	....
5: 46 p. m.	102	....
5: 48 p. m.	...	0.12
6: 15 p. m.	83	....
6: 30 p. m.	78	....
6: 56 p. m.	...	0.08
7: 40 p. m.	87	....
7: 57 p. m.	...	0.08
8: 40 p. m.	105	....
9: 00 p. m.	...	0.08
9: 20 p. m.	112	....
9: 40 p. m.	118	....
10: 00 p. m.	...	0.1
10: 30 p. m.	101	....
10: 48 p. m.	101	....
11: 11 p. m.	105	....

TABLE 2.—*Fasting Morning Blood Sugar in Depancreatized Dogs Without Insulin to Cover the Night Requirement*

Dog	Blood Sugar, Mg. per 100 Cc.
1	440
2	348
3	400
4	400
5	286
6	336
7	270
8	400
9	364
10	400
11	400

in which this basal insulin requirement was controlled in a fasting dog by the injection of a small amount of insulin at a constant rate are recorded in table 1. If such insulin is not supplied, the fasting blood sugar values in dogs vary from 300 to 500 mg. per hundred cubic

centimeters, as indicated in table 2. The rising blood sugar of the fasting depancreatized dog without insulin may result from the increased metabolism of body protein that is known to occur during the fasting state in the normal as well as in the depancreatized dog [5] or from hepatic glycogenolysis. Mirsky [6] stated that one generally accepted function of insulin is its ability to inhibit glycogenolysis induced by various means. This action has been demonstrated by the work of Major and Mann,[7] who found that the liver of the depancreatized dog can form glycogen when dextrose is given in large amounts but cannot retain it unless insulin is given simultaneously. The dietary requirements of the depancreatized dog are best met by the use of regular insulin, which, as indicated in chart 1, has a period of activity most suitable for the absorption curve of carbohydrate after a meal.[8] Protamine zinc insulin, with its

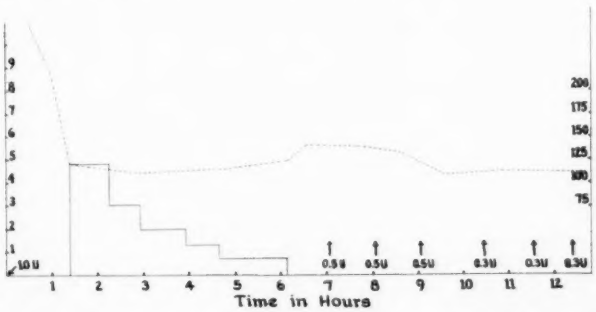


Chart 1.—Insulin activity in a depancreatized dog. The dotted line represents blood sugar in milligrams per hundred cubic centimeters of blood. The area enclosed by the solid line represents grams of dextrose given intravenously per hour. The arrows represent times of intravenous injection of regular insulin in amounts as charted.

slower, more prolonged effect,[9] is more suited to cover the basal insulin requirement.

The observations in depancreatized dogs, it is true, are not always applicable to the diabetic patient, but our experience with animals has

5. Lusk, G.: The Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928.

6. Mirsky, I. A.: The Site and Mechanism of the Antiketogenic Action of Insulin, Am. J. Physiol. **116**:322-326 (July) 1936.

7. Major, S. G., and Mann, F. C.: The Formation of Glycogen Following Pancreatectomy, Am. J. Physiol. **102**:409-421 (Nov.) 1932.

8. Drury, D. R., and Greeley, P. O.: The Rate of Disappearance of Insulin from the Body, abstracted, Am. J. Physiol. **126**:481-482 (July) 1939; Proc. Am. Physiol. Soc., 1939, pp. 65-66.

9. Himsworth, H. P.: Protamine Insulin and Zinc Protamine Insulin in the Treatment of Diabetes Mellitus, Brit. M. J. **1**:541-546 (March 13) 1937.

led us to believe that by determinations of the basal insulin rate of human beings we might elicit in a comparatively simple way a procedure which would result in more accurate calculations of insulin requirements. If such a procedure could be evolved, many days of trial and error would be saved and a more nearly mathematical calculation would be possible.

The application of the concept of a basal insulin requirement to the diabetic patient has received little attention except by the French workers Baudouin, Lewin and Azérad.[10] They stated that normal dogs require 0.05 unit of insulin per kilogram per hour intravenously to produce hypoglycemia. They estimated the normal pancreatic secretion in human beings in the fasting state to be 0.005 unit per kilogram per hour. To reduce the blood sugar to normal in persons with severe diabetes 0.2 to 0.4 unit of insulin per kilogram per hour is necessary. To maintain the blood sugar at a normal level in persons with severe diabetes while fasting 0.01 unit per kilogram per hour is necessary. Lawrence[11] also

TABLE 3.—*Elevation of Fasting Blood Sugar*

Time	Insulin, in Units	Diet, in Grams			Blood Sugar, Milligrams per Hundred Cubic Centimeters
		Carbohydrate	Protein	Fat	
6 p. m.	20	20	25	40	224
8 p. m.	..	..	..	..	171
10 p. m.	..	..	..	..	89
12 p. m.	..	..	..	..	89
4 a. m.	..	..	..	..	90
8 a. m.	..	..	..	..	321

appears to have been cognizant of the basal insulin requirement in the person with severe diabetes, as he stated that the sudden elevation of the blood sugar from endogenous sources is no exceptional phenomenon. He frequently observed patients whose blood sugar was about 0.08 per cent late in the evening and over 0.3 per cent the next morning. One case cited by him illustrates this (table 3).

DIVISION OF DIABETIC PATIENTS INTO THOSE WITH AND THOSE WITHOUT A BASAL INSULIN REQUIREMENT

It is axiomatic to state that a patient who receives regular insulin, remains sugar free throughout the day and has a normal blood sugar in

10. Baudouin, A.; Lewin, J., and Azérad, E.: Injections lentes et continues d'insuline chez les diabétiques, Presse méd. **46**:729-732 (May 7) 1938; Injections continues d'insuline chez les diabétiques. Dose nécessaire pour ramener la glycémie à la normale, Compt. rend. Soc. de biol. **127**:378-380 (Feb. 5) 1938; Injections intraveineuses continues d'insuline. Recherche de la dose d'entretien chez trois diabétiques, ibid. **127**:380-382 (Feb. 5) 1938.

11. Lawrence, R. D.: Studies of an Insulin-Resistant Diabetic, Quart. J. Med. **21**:359-369 (April) 1928.

the early morning before breakfast will have no basal insulin requirement as defined in this paper. In fact, this may be said to be the goal of diabetic therapy, but, as is well known, such a goal is not always attainable if the somewhat hazardous insulin shock is to be avoided. A simple procedure actually will decide which diabetic patients have a basal insulin requirement. This is done by determining the fasting morning blood sugar under the following conditions: no sugar in the urine four to six hours after the evening meal, which has been adequately covered by regular insulin, and no protamine zinc insulin for twenty-four hours. Diabetic patients with high renal thresholds will require in addition a normal blood sugar content six hours after the evening meal. With

TABLE 4.—*Determination of Presence or Absence of Basal Insulin Requirement*

Case	Sex	Age	Insulin Given, in Units	Urine Sugar, s. p. m.	Fasting Morning Blood Sugar, Mg. per 100 Cc.	Basal Insulin Required
1	M	19	20- 5-10	Negative	142.8	No
2	F	44	45-35-30	Negative	167.0	Yes
3	F	20	20- 0-15	?	235.0	Yes
4	M	20	10-10-10	Negative	167.0	Yes
5	M	48	25-10-10	Negative	160.0	Yes
6	F	56	None	Negative	91.0	No
7	M	23	15-15-15	Negative	156.2	Yes
8	F	61	10-10-10	Negative	208.0	Yes
9	M	56	40 protamine zinc insulin in a. m. 10 and 15 protamine zinc insulin in a. m.	Negative	109.9	No
10	F	72	15-15-15	Negative	124.2	No
11	F	57	10- 0-10	Negative	173.9	Yes
12	F	24	15-10-15	Negative	142.8	No
13	F	38	20-20-20	Negative	133.3	No
14	F	38	15-10-10	Negative	121.2	No
15	M	41	10- 0-10	Negative	109.9	No
16	F	66	20- 0-20	Negative	119.0	No
17	F	58	None	Negative	105.0	No

such requirements fulfilled, a fasting morning blood sugar of 150 mg. or more per hundred cubic centimeters indicates the necessity for insulin to cover the basal requirement. The results obtained in a series of diabetic patients in the diabetic service of the Los Angeles County Hospital are presented in table 4.

METHOD OF DETERMINING THE BASAL INSULIN REQUIREMENT

If it is decided that a patient has a basal insulin requirement the procedure is as follows: Whenever possible the fasting blood sugar is brought to a level between 100 and 150 mg. per hundred cubic centimeters on the morning of the test by the use of regular insulin six to seven hours previously (midnight), in amounts varying from 5 to 25 units. The exact amount given at midnight depends on the severity of the condition—the patients with least severe diabetes taking 5 units; those with moderately severe, 10 to 20 units, and those with the most

severe, 20 to 30 units. (The Folin-Wu micro blood sugar method with 0.1 cc. of oxalated venous blood is used because of its convenience in making frequent determinations, although this method gives slightly lower readings than the usual Folin-Wu method). The blood sugar is determined every half-hour to every hour for six or seven hours for the subject who has fasted for twelve hours and has had no protamine zinc insulin for twenty-four to thirty hours. Regular insulin is given subcutaneously every hour in the amount estimated to keep the blood sugar between 100 and 150 mg. per hundred cubic centimeters. The exact amount of insulin required is often difficult to gage, but practice makes the problem easier. In general, however, it has been found that a patient who has been using 50 to 60 units of insulin or less daily has a basal insulin requirement of 1 unit or less per hour; one who has been using between 60 and 100 units of insulin daily has a basal requirement of 1 to 2 units per hour, and one who has been using over 100 units of insulin daily has a basal requirement of 3 to 4 units per hour. With this as a general scheme, it is easy to make individual adjustments, for if the level of the hourly blood sugar is rising the amount of the hourly dose of insulin should be increased, or it should be decreased if the blood sugar level is dropping. As regular insulin exerts an effect for six to seven hours, the cumulative effect of hourly injections must be borne in mind.

The following records have been selected from a group to illustrate the procedure and the results of basal insulin determinations.

REPORT OF CASES

CASE 1 (case 6, table 4).—S. B., a white woman aged 58, had a history of long-standing mild diabetes. On admission she complained that the diabetes was out of control and that she had precordial pain. She had had no special diet or insulin prior to entry. Her fasting blood sugar twenty-four hours after admission was 214 mg. per hundred cubic centimeters. She was given insulin and a diet to control the condition. After two weeks the administration of insulin was discontinued, and the condition was controlled with a diet of 100 Gm. of carbohydrate, 60 Gm. of protein and 80 Gm. of fat per day.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Insulin
8: 35 a. m.	91.0	None
10: 25 a. m.	91.0	
10: 50 a. m.	80.0	
11: 55 a. m.	75.5	

This patient represents the very mildly diabetic person, who requires no basal insulin and no dietary insulin.

CASE 2 (case 1, table 4).—R. B., a white youth aged 19, had had diabetes for one year. He had had 25 units of protamine zinc insulin daily, but little attention had

been paid to his diet. He was admitted to the hospital with a severe insulin reaction. The condition was controlled by a diet consisting of 300 Gm. of carbohydrate, 80 Gm. of fat and 90 Gm. of protein per day, with insulin before each meal in doses of 10, 13 and 10 units.

Basal Insulin Study

Time	Blood* Sugar, Milligrams per Hundred Cubic Centimeters	Insulin
8: 00 a. m.	105.0	None
9: 50 a. m.	95.0	
11: 45 a. m.	137.9	
1: 45 p. m.	111.1	
3: 30 p.m.	95.0	

* Capillary blood was used for determinations.

This patient required insulin to cover the diet but had no basal insulin requirement.

CASE 3.—J. Z., a white man aged 27, was admitted to the hospital in diabetic coma. He had had 80 units of protamine zinc insulin per day during the six months prior to entry, but his diet had not been carefully measured. Several days after the acidosis was controlled, the basal insulin requirement was determined.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
7: 00 a. m.	123.5	4
7: 30 a. m.	135.0	..
8: 00 a. m.	144.0	..
8: 30 a. m.	128.0	2
9: 00 a. m.	119.0	..
9: 30 a. m.	133.3	1.5
10: 00 a. m.	118.0	....
10: 30 a. m.	118.0	1.5
11: 00 a. m.	102.5	....
11: 30 a. m.	87.0	1.5
12: 00 a. m.	81.7	....
12: 30 p. m.	81.7	....

Fifteen units of regular insulin was given at midnight before the morning of the test in order to have the fasting blood sugar under 150 mg. per hundred cubic centimeters. Protamine zinc insulin was not given prior to the study because of its prolonged effect.

As seen by the basal insulin study, this patient had a basal insulin requirement of 1 to 1.5 units per hour. To cover the night requirement of eight to ten hours 15 units of protamine zinc insulin (8 to 10 hours $\times$ 1.5 units per hour) was given at bedtime. The insulin requirement during the day was met by the insulin given to cover the diet. After the study the condition was well controlled with 10 units of regular insulin before each meal plus 15 units of protamine zinc insulin at bedtime, in addition to a daily diet of 150 Gm. of carbohydrate, 60 Gm. of protein and 75 Gm. of fat.

This patient represents a person with moderately severe diabetes, with a basal insulin requirement of 1 to 1.5 units per hour.

CASE 4.—U. T., a white woman aged 18, entered the hospital with a fracture of the left wrist and the complaint that her diabetes was out of control. She was known

to have had diabetes since she was 14. Prior to entry she had been taking 50 units of protamine zinc insulin and 30 units of regular insulin before breakfast, with a diet of 100 Gm. of carbohydrate, 60 Gm. of protein and 80 Gm. of fat per day. There was 2 to 3 per cent sugar in twenty-four hour urine while she was on this regimen. Her blood sugar on entry was 308 mg. per hundred cubic centimeters. The basal insulin requirement was determined.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
7: 35 a. m.	118.0*	..
7: 40 a. m.	.....	5
9: 05 a. m.	105.0	..
10: 12 a. m.	86.0	..
10: 45 a. m.	110.0	..
11: 53 a. m.	110.0	..
11: 55 a. m.	.....	1
12: 49 p. m.	120.5	..
12: 52 p. m.	.....	1
1: 47 p. m.	105.0	..

* Capillary blood was used for this determination. Venous blood was used for the other determinations.

Fifteen units of regular insulin was given at bedtime the night before the study to bring the fasting morning blood sugar to a normal level. (The 5 units given at first was too much, as no further insulin was required for four hours.)

The patient had a basal requirement of 1 unit per hour. The night requirement thus was about 10 units of protamine zinc insulin at bedtime (8 to 10 hours × 1 unit per hour). The insulin requirement during the day was covered by the dietary insulin.

After study the patient was placed on a diet of 100 Gm. of carbohydrate, 75 Gm. of protein and 60 Gm. of fat per day with 20 units of regular insulin before breakfast, 15 units before lunch and 15 units before dinner and with 15 units of protamine zinc insulin at bedtime. The condition was controlled excellently.

The night basal requirement was determined to be 8 to 10 units, but this was increased to 15 units because of moderate glycosuria after breakfast.

This patient is another illustration of a person with moderately severe diabetes, with a basal insulin requirement of 1 unit per hour.

Case 5 (case 7, table 4).—P. Q., a white man aged 23, was admitted to the hospital with diabetic acidosis and bronchopneumonia. He had been known to have diabetes for one week but had symptoms of one year's duration. The basal insulin requirement was determined after the pneumonia had subsided.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
8: 10 a. m.	173.9	1.5
9: 00 a. m.	210.5	2
10: 00 a. m.	204.1	2
10: 55 a. m.	200.0	2
12: 00 m.	.....	2
12: 40 p. m.	163.9	...
1: 16 p. m.	.....	2
1: 18 p. m.	169.5	...

He was given 15 units of regular insulin at midnight before the test to bring the fasting morning blood sugar to a normal level. He should have had 20 to 25 units, as his fasting morning blood sugar was 173.9 mg. per hundred cubic centimeters.

The patient was found to have a high basal insulin requirement, almost 2 units per hour. The night requirement is 15 to 20 units of protamine zinc insulin (8 to 10 hours $\times$ 2 units per hour). The insulin requirement during the day is covered by the dietary insulin. After study the patient was given 25 units of protamine zinc insulin at night (the dose was later decreased to 15 units), and with this regimen the fasting morning blood sugar was 109 mg. per hundred cubic centimeters.

At the time this study was made the patient had been afebrile from his pneumonia for four to five days, but a productive cough persisted. With the subsidence of infection the basal requirement of insulin will probably decrease. The condition had not been controlled in the ward until insulin was given at night to cover the basal requirement.

This patient is a good example of those who have a high basal insulin requirement, 2 units per hour.

CASE 6 (case 2, table 4).—M. F., a white woman aged 44, stated on admission to the hospital that her diabetes was out of control and complained of dry gangrene on the tip of the left great toe. She had severe diabetes and had been hospitalized several times because of acidosis. The condition had never been adequately controlled until the basal insulin requirement was determined.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
6: 30 a. m.	148.0	3
7: 30 a. m.	150.0	3
8: 30 a. m.	126.7	3
9: 30 a. m.	130.7	3
10: 30 a. m.	135.0	3
11: 30 a. m.	137.9	3

She was given 20 units of regular insulin at midnight before the test to bring the fasting blood sugar to a normal level.

The basal insulin rate was found to be 3 units per hour. The night requirement was thus 25 to 30 units (8 to 10 hours $\times$ 3 units per hour). The insulin requirement during the day was covered by the dietary insulin. After study the patient was stabilized on a diet of 150 Gm. of carbohydrate, 75 Gm. of protein and 100 Gm. of fat per day, with 45 units of regular insulin before breakfast, 35 units before lunch and 30 units before dinner and 20 units of protamine zinc insulin at bedtime. At first 40 units of protamine zinc insulin was given at bedtime for the night requirement, but this dose was gradually decreased to 20 units. The increased amount was given to aid in controlling the glycosuria which occurred after breakfast.

This patient is an example of the diabetic person who has a high basal insulin rate, 3 units per hour, and a high dietary insulin requirement.

THERAPEUTIC USEFULNESS AND ILLUSTRATIVE RECORDS

The determination as to whether or not a patient has a basal insulin requirement is simple and can be done easily. The actual determination

may at first appear to be an expensive, laborious procedure, primarily of academic interest. With practically all patients studied these factors have been more than compensated for by the decrease in time necessary to establish control in difficult problems or the decrease in total insulin dosage for twenty-four hours, when the right type and spacing of insulin are used.

The criticism will doubtless be raised that four injections daily are required for the control of severe diabetes, and that this is merely a step backward to the regimen advocated in the early days of insulin. However, the advantages of multiple injections of insulin over the single dose are well known. Joslin [12] stated: "The more frequently insulin is given, the less is required to produce the same result, because of adjustments to temporary requirements. Holm showed this beautifully with depancreatized dogs." The inconvenience of the four injections daily is, in our opinion, more than counterbalanced by more adequate control of the condition and reduction of the total insulin requirement frequently attained. It should be emphasized that we are not advocating this regimen for all persons with diabetes, since the majority of patients can be controlled by one or two injections of regular insulin or protamine zinc insulin daily. Rather than a reversion to an old regimen, we feel that the concept of a basal insulin requirement is a new step forward. The old four injection regimen was more or less a "hit or miss" method which was found to be useful but had little rational basis. Consideration of the problem from the standpoint of basal insulin requirement provides a scientific foundation for insulin therapy. Determination of the dosage and time of administration of insulin then become logical. This is essentially the substitution of a rational method for an empiric method

Patients who have a basal insulin requirement of 1 unit or more per hour require insulin to cover the entire twenty-four hours of the day, in addition to that necessary for covering the dietary intake. The importance of an insulin activity twenty-four hours of the day in the person with severe diabetes has been stressed by Wilder [13] in a study of the urinary nitrogen excretion in patients with diabetes. He emphasized the point that in severe diabetes azoturia and creatinuria are restrained only during the period of activity of the injected insulin. As regular insulin exerts an effect during a period of from six to seven

12. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1937.

13. Wilder, R. M.: Clinical Investigation of Insulins with Prolonged Activity, Ann. Int. Med. **11**:13-29 (July) 1937.

hours (this has been demonstrated by many laboratories), the amount given before meals can be adjusted to cover the insulin requirement in the waking hours. The activity of regular insulin in a diabetic subject is indicated in chart 2. As the peak of activity of regular insulin is within the first two to three hours after injection, this type of insulin is unsuited to requirements during the night, when an insulin exerting a plateau type of activity is most desirable. This activity is best obtained by protamine zinc insulin. For dietary control regular insulin is the correct agent, since its activity curve conforms more closely to the absorption curve of carbohydrate after a meal (chart 2). The activity of regular insulin in a diabetic patient is similar to its action in a depancreatized dog (chart 1). Protamine zinc insulin in our experience [14] has been found unsuited for this dietary requirement in persons with severe

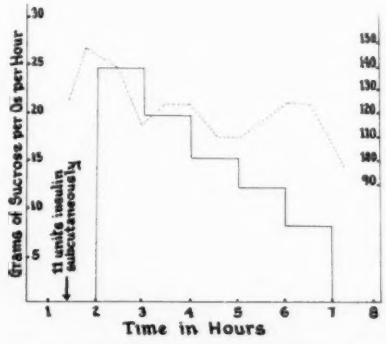


Chart 2.—Insulin activity. The dotted line represents blood sugar in milligrams per hundred cubic centimeters. The area enclosed by the solid line represents grams of sucrose given per os per hour. The arrow represents the time of subcutaneous injection of regular insulin.

diabetes, owing to the difficulty in spacing the food intake to cover the period of maximum activity of the protamine zinc insulin without periods of hypoglycemia. This point, as indicated before, will be considered debatable by many, since Joslin [12] stated that protamine zinc insulin is effective in 95 per cent of persons with diabetes. Still, there are indications in his textbook and elsewhere [15] that difficulties in controlling severe diabetes with protamine zinc insulin alone have been encountered. Wilder [13] noted that the blood sugar is more unstable in patients who

14. Martin, H., and Greeley, P. O.: The Problem of Protamine Zinc Insulin Therapy, to be published.

15. Mosenthal, H. O., and Mark, M. F.: The Prolonged Use of Protamine Zinc Insulin, J. A. M. A. **113**:17-22 (July 1) 1939.

are given protamine zinc insulin when much carbohydrate is included in the diet. The action of each of these types of insulin and the difference in their activities is illustrated by a comparison of chart 3, in which may be seen a curve indicating the activity of protamine zinc insulin in a diabetic patient, with chart 2, which shows the activity of regular insulin in a diabetic patient. In persons with severe diabetes the two roles played by insulin, control of the dietary intake and control of the basal requirement, are provided most satisfactorily by the use of regular insulin to cover the diet and protamine zinc insulin to cover the basal insulin requirement. With knowledge of the basal requirement and of the activity of a given amount of insulin in controlling carbohydrate, patients whose diabetes was previously inadequately controlled have been stabilized easily. (The determination of the amount of insulin necessary to cover the diet will not be discussed in this paper, as it is the subject of

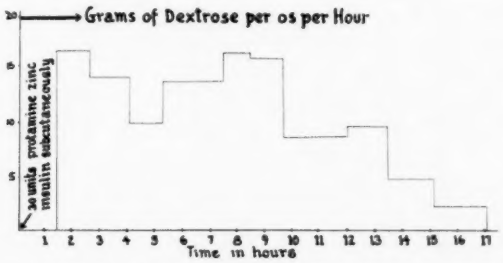

Grams of Dextrose per os per Hour
30 units protamine zinc insulin subcutaneously
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Time in hours

Chart 3.—Protamine zinc insulin activity. The area enclosed by the solid line represents grams of dextrose given per os per hour, corrected for errors in failure to maintain the blood sugar level at 100 mg. per hundred cubic centimeters of blood. The arrow represents the time of subcutaneous injection of protamine zinc insulin.

another article,[16] but the method by which the activity of a given amount of insulin is determined by repeated blood sugar determinations after ingestion of dextrose is merely a refinement of the method ordinarily followed in adjusting the dietary insulin to cover postprandial glycosuria). The control of severe diabetes in 2 patients by such methods is illustrated by detailed protocols.

CASE 6.—Before detailed study the patient (a white woman aged 44) excreted 3.33 per cent, or 52.8 Gm., of sugar in the urine during twenty-four hours when the diet contained 150 Gm. of carbohydrate, 60 Gm. of protein and 80 Gm. of fat, and she received 40 units of regular insulin before breakfast, 25 units before lunch, 25

16. Drury, D. R., and Martin, H.: The Activity of Insulin with Carbohydrate, to be published.

TABLE 5.—*Diabetic Control in Case 6*

Time	Blood Sugar, Mg. per 100 Cc.	Diet, Gm.			Insulin, Units	Urine, Cc.	Total Sugar in Urine, Gm.
		Carbohydrate	Protein	Fat			
11: 00 a. m.	133	...	..	...	35 (regular)	...	....
11: 35 a. m.	.....	35	30	40	...	...	....
1: 55 p. m.	110	15	..	...	...	...	....
3: 55 p. m.	103	...	..	...	...	650	1.85
4: 00 p. m.	.....	...	..	...	30 (regular)	...	....
4: 30 p. m.	.....	35	30	40	...	...	....
8: 00 p. m.	.....	...	..	...	...	500	0.695
8: 55 p. m.	122.6	15	..	...	...	...	....
11: 50 p. m.	.....	8	10	12	20 (protamine zinc)	...	....
2: 00 a. m.	128	..	..	...	...	...	....
6: 00 a. m.	160	...	..	...	...	300	0.61
7: 00 a. m.	.....	...	..	...	45 (regular)	...	....
7: 30 a. m.	.....	35	15	20	...	...	....
9: 00 a. m.	181.8	...	..	...	...	...	....
10: 00 a. m.	.....	15	..	...	...	300	1.7
10: 50 a. m.	129	...	..	...	...	...	....
Total..		158	85	112	130		4.85

TABLE 6—*Diabetic Control of Patient 3*

Time	Blood Sugar, Mg. per 100 Cc.	Diet, Gm.			Insulin, Units	Urine, Cc.	Total Sugar in Urine, Gm.
		Carbohydrate	Protein	Fat			
12: 00 p. m.	...	...	..	...	10 (protamine zinc)	...	....
	...	...	..	...	10 (regular, by error)	...	....
6: 00 a. m.	...	...	..	...	...	1,300	0
6: 45 a. m.	80	...	..	...	10 (regular)	...	....
7: 00 a. m.	...	50	12	15	...	...	....
9: 15 a. m.	164	...	..	...	...	...	....
10: 40 a. m.	180	...	..	...	10 (regular)	600	3.4
11: 10 a. m.	...	50	24	30	...	...	....
1: 15 p. m.	143	...	..	...	...	200	1.9
3: 00 p. m.	125	..	..	...	...	625	2.85
4: 00 p. m.	...	...	..	...	10 (regular)	...	....
4: 30 p. m.	...	50	24	30	...	...	....
8: 00 p. m.	...	...	..	...	...	1,600 cc.	0
12: 00 p. m.	...	...	..	...	15 (protamine zinc)	...	....
6: 00 a. m.	...	...	..	...	...	1,000	0
Total..		150	60	75	65		8.15

units before dinner and 20 units at midnight. This represented a dextrose-insulin ratio of 1.11.

Carbohydrate in diet	Carbohydrate, 150 Gm. Carbohydrate from protein, 34 Gm.	= 184 Gm.
Carbohydrate lost in urine		52 Gm.
Carbohydrate used		132 Gm.
Total insulin used		110 units

The basal insulin requirement was found to be 3 units per hour. She was placed on a diet of 150 Gm. carbohydrate, 75 Gm. protein and 100 Gm. of fat daily, with 45 units of insulin before breakfast, 35 units before lunch and 30 units before dinner and 20 units of protamine zinc insulin at bedtime. With this dietary and insulin regimen the urinary sugar was practically nil. This represents a dextrose-insulin ratio of 1.5.

Carbohydrate in diet	Carbohydrate from protein, 44 Gm. Carbohydrate, 150 Gm.	= 194 Gm.
Carbohydrate lost in urine		5 Gm.
Carbohydrate used		193 Gm.
Total insulin used		130 units

The excellent control with such a regimen is indicated by the figures in table 5.

CASE 3.—The patient entered the hospital in diabetic coma. He had been receiving 80 units of protamine zinc insulin daily before entry. His diet had not been carefully followed. The basal insulin requirement of this patient (a white man aged 27) was found to be 1 to 1.5 units per hour. The excellent control obtained by the addition of insulin at night to the dietary insulin is recorded in table 6. His diet consisted of 150 Gm. carbohydrate, 60 Gm. protein and 75 Gm. of fat daily, with 10 units of regular insulin before each meal and 15 units of protamine zinc insulin at midnight.

SUMMARY

The basal insulin requirement is defined as the amount of insulin necessary to prevent hyperglycemia and glycosuria in the postabsorptive or fasting state.

A simple method has been given by which persons with diabetes may be classified as to their basal insulin requirement.

The detailed method by which the basal insulin requirement is determined has been explained, and some records of studies made on patients have been presented as illustrations.

The therapeutic usefulness of the application of this principle to the control of severe diabetes not well controlled on other regimens has been emphasized.

Protamine zinc insulin given at night has been suggested as the insulin most suited to cover the basal insulin requirement, while regular insulin is most suited to cover the dietary intake in persons with severe diabetes.

THE ELECTROCARDIOGRAM IN INSULIN SHOCK

DOUGLAS GOLDMAN, M.D.
CINCINNATI

The use of extreme states of insulin shock in the treatment of psychiatric patients, particularly of those with schizophrenia, has in the last few years afforded an opportunity to study electrocardiographic changes in presumably normal hearts under the influence of large doses of insulin. Insulin shock therapy was introduced by Sakel [1] in 1933 for patients with hitherto relatively hopeless schizophrenia. After a preliminary period of suspicious aloofness, psychiatrists and physicians interested in mental disease have adopted the method on a large scale because of the brilliant results at times achieved.

The method and technic are given in detail in Sakel's monograph and elsewhere. The usual technic requires patients to be in coma from hypoglycemia for an hour or more. This means that from the time the insulin is injected to the termination of the coma three to five hours elapses, during which severe hypoglycemia is present, with minimum blood sugar values of 10 to 30 mg. per hundred cubic centimeters.

Several studies of the electrocardiogram in insulin shock therapy have been reported, but the only one of adequate proportions is that of Hadorn.[2] Some of his observations and conclusions are not in complete agreement with mine. Earlier work by Edwards and Page,[3] Bucka, Friedländer and Schäffer,[4] Soskin, Katz, Strouse and Rubinfeld [5] and numerous others has preempted any priority that may be claimed for description of individual changes in the electrocardiogram during insulin

From Longview State Hospital, Dr. E. A. Baber, Superintendent.

Some of the insulin used in this work was supplied by Eli Lilly & Co. and by E. R. Squibb & Sons.

1. Sakel, M.: Pharmacological Shock Treatment of Schizophrenia, translated by J. Wortis, Nervous and Mental Disease Monograph 62, Washington, D. C., Nervous and Mental Disease Publishing Company, 1938.

2. Hadorn, W.: Untersuchungen des Herzens im hypoglykämischen Schock, Arch. f. Kreislaufforsch. **2**:70, 1937.

3. Edwards, D. J., and Page, I. H.: Observations on the Circulation During Hypoglycemia from Large Doses of Insulin, Am. J. Physiol. **69**:177, 1924.

4. Bucka, E.; Friedländer, K., and Schäffer, H.: Ueber die Einwirkung des Insulins und der Hypoglykämie auf das menschliche Herz, Nach elektrokardiographische Untersuchungen, Ztschr. f. d. ges. exper. Med. **57**:35, 1927; cited by Hadorn.[2]

5. Soskin, S.; Katz, L. N.; Strouse, S., and Rubinfeld, L. H.: Treatment of Elderly Diabetics with Cardiovascular Disease, Arch. Int. Med. **51**:122 (Jan.) 1932.

shock. Of particular interest in this respect is the work of Bucka, Friedländer and Schäffer. Other writers have described numerous instances of untoward clinical effects of insulin on the heart in patients with diabetes, such as anginal attacks [6] and auricular fibrillation.[5] No complete survey of the literature on the effect of insulin on the electrocardiogram will be attempted in this essay.

The chief interest in the recent investigations of the effects on the electrocardiogram in purposefully produced insulin shock is derived from the practically ideal experimental conditions of the treatment, the normal quality of the hearts investigated and the deliberate chronicity with which the treatment is carried out, in spite of what might be considered dangerous and threatening symptoms.

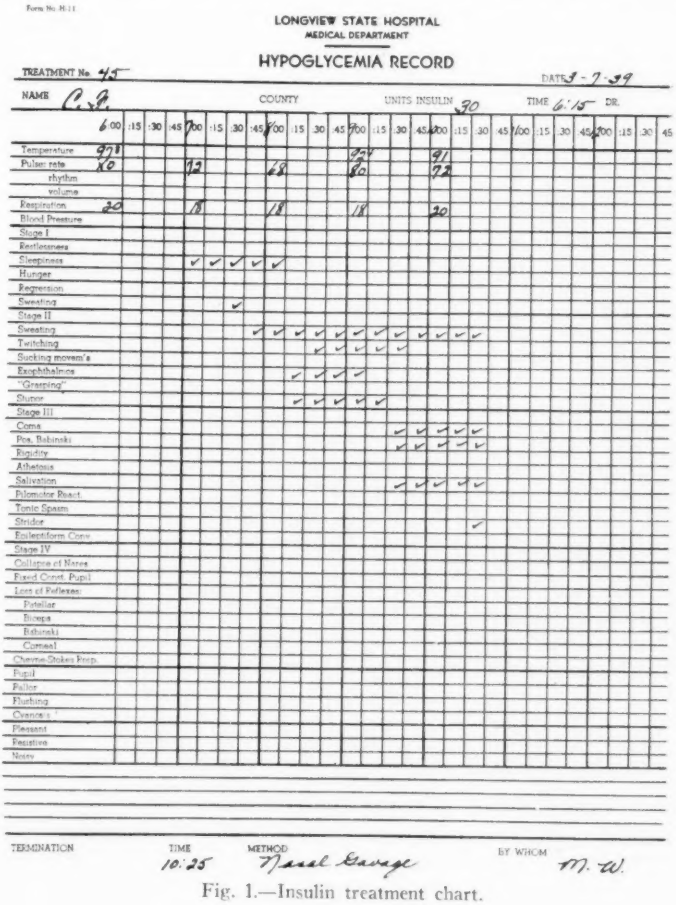
METHOD OF INVESTIGATION

Two groups of patients were studied. Eleven patients who received insulin shock therapy by the classic Sakel technic were investigated electrocardiographically from time to time throughout their period of treatment and at intervals for several months afterward. Tracings were made periodically before the day's injection, again at the fastigium of the treatment in stage 3 or 4 (fig. 1) and often again the following morning before the treatment. Rest days were taken into consideration, as indicated in individual studies. The other group consisted of 7 patients who received huge doses of protamine zinc insulin. The dose varied from 50 to 300 units and was given in two equal parts with intervals of twelve hours. The patients were often hypoglycemic but almost never comatose and were up and about practically all the time. Complete study of this group will be published separately. Tracings were made at intervals in the morning before the first dose of insulin and the morning meal and occasionally at other times of the day. This group of patients was also followed for several months after cessation of treatment. Control tracings before initiation of treatment were taken in both groups. A total of some 600 tracings was obtained and studied. It is to be noted that no digitalis or other "cardiac" drug was administered at any time to the patients.

An amplifier tube apparatus (cardiette) was used throughout the investigation. The three classic leads and one chest lead were recorded in every case with rare exceptions necessitated by circumstances. The chest lead was recorded with the right arm electrode in the fourth intercostal space just to the left of the sternum and the left leg electrode in place as the "indifferent" electrode. Most of the tracings were recorded before the publication of the standardized placement of chest electrodes

6. Turner, K. B.: Insulin Shock as the Cause of Cardiac Pain: Case Report, Am. Heart J. **5**:671, 1930.

decided by the American and British Heart Associations, and the routine for the purposes of this study was not changed. The condition of the patients in deep insulin shock made recording of acceptable tracings difficult at times, but patience usually surmounted these difficulties


LONGVIEW STATE HOSPITAL
MEDICAL DEPARTMENT
HYPOGLYCEMIA RECORD
TREATMENT No. 45
DATE 3-7-39
NAME C. S.
COUNTY
UNITS INSULIN 70
TIME 6:15 DR.
Temperature 97.8 97.4 97.4 97.4

and voltage produced by insulin will be taken up systematically; second, the progression of these changes as a whole throughout the weeks of treatment will be considered. In this way a true picture of conditions will be more readily demonstrated.

Physical signs were investigated in these patients, but no outstanding or noteworthy evidence of insulin effect on the heart was determined. Changes in rhythm were detectable at times but were much more striking in the electrocardiograms. The blood pressure regularly rose in most cases from 10 to 30 mm. of mercury (table 1). No instance of heart failure has occurred in over 12,000 shock treatments in more than 200 patients, nor has there been any evidence of subsequent circulatory embarrassment.[7] Rarely during the coma apparent circulatory collapse with lowered blood pressure occurs, but this has always responded to treatment with sugar given intravenously.

TABLE 1.—*Blood Pressures Before, During and After Insulin Shock*

Patient	Before Insulin 6:00 a. m.	Two Hours 8:00 a. m.	Three Hours 9:00 a. m.	Four Hours 10:00 a. m.	After Termination of Shock Treatment
S. S.	108/	115/65	150/90	160/90	140/95
G. B.	124/88	140/70	160/85	165/95	120/70
R. H.	134/90	150/80	150/75	160/90	145/85
R. T.	124/90	145/80	160/80	160/90	140/80
C. R.	120/80	150/80	.....	.....	105/85
M. O.	120/80	135/75	150/75	.....	130/80
H. M.	128/80	154/80	158/80	155/95	140/85
R. P.	140/90	150/60	162/82	166/76	152/78
R. D.	126/76	129/60	128/82	160/80	170/110
L. M.	100/40	134/74	146/88		

Either bradycardia or tachycardia may occur in insulin shock. The effect of insulin on the heart rate depends largely on other effects of the insulin in the person. The patients who show severe and frequent tonic spasms, epileptiform seizures, marked athetosis or other forms of motor hyperactivity have tachycardia, usually of sinus origin but occasionally of other types (fig. 2). When the shock produces marked fall in body temperature (sometimes to as low at 90 F.) and reduction in general metabolic activity, bradycardia is to be expected. Tachycardia may persist for some time after the cessation of the shock, but bradycardia usually gives way to the normal rate when the shock is terminated.

Auricular flutter and auricular fibrillation (fig. 2) are rare occurrences. In my experience they have always been transient and without any recognizable clinical effect. Extrasystoles are occasionally observed during insulin shock. In only 3 instances were they observed by Hadorn in his series, in 2 of which they were ventricular and in 1

7. Since this was written 1 patient died suddenly during coma. Autopsy showed numerous minute hemorrhages in the brain and dilatation of the right side of the heart.

auricular. In the present series several instances were observed (fig. 3). It should be noted that "shock" is not a necessary condition for production of extrasystoles, for the most striking examples are observed in the tracings of 2 patients receiving protamine zinc insulin (fig. 3).

The sinuauricular mechanism often undergoes marked changes with consequent disturbance in rhythm. Respiratory sinus arrhythmia does not seem of serious significance in the age group usually subjected to this treatment. Suppression of the normal activity of the sinus node is a frequent result of insulin hypoglycemia and manifests itself in various ways. Bradycardia with abnormal or suppressed P waves suggests activity of rhythm centers more primordial above the node ("sino-

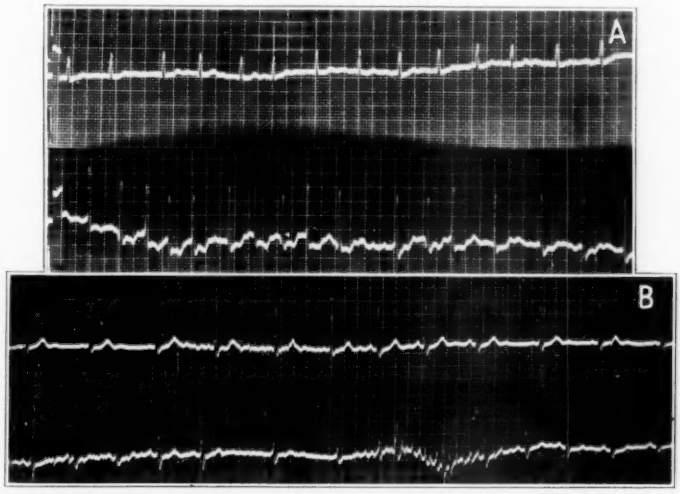


Fig. 2.—Electrocardiograms of A. S. *A*, leads I and II, auricular flutter with occasional dropped beat; thirteenth treatment, stage 3; 50 units of insulin, 17 mg. sugar per hundred cubic centimeters of blood, temperature 95 F. *B*, leads II and III, transient auricular fibrillation; forty-first treatment, stage 3; 45 units of insulin, blood sugar 11 mg. per hundred cubic centimeters, temperature 96 F.

Kaudaler rhythmus") (fig. 4). Failure of appearance of the P wave, with a long pause followed by a normal ventricular complex, indicates complete though transient sinuauricular block with ventricular escape (fig. 4). Instances of periodic recurrence of ventricular escape with undulating changes in the intervening P waves (fig. 4 *B*) indicate fluctuations in the degree of sinuauricular block which may be quite analogous to the "Wenckebach periods" of low grade auriculoventricular block. It is noteworthy that Hadorn stated that he did not observe instances of sinuauricular block in his studies.

Increased auricular irritability is manifested in the occurrence of premature auricular contractions (fig. 3), auricular flutter (fig. 2) and auricular fibrillation (fig. 2). These have been transient in the present series, have required no treatment and have resulted in no clinical difficulty.

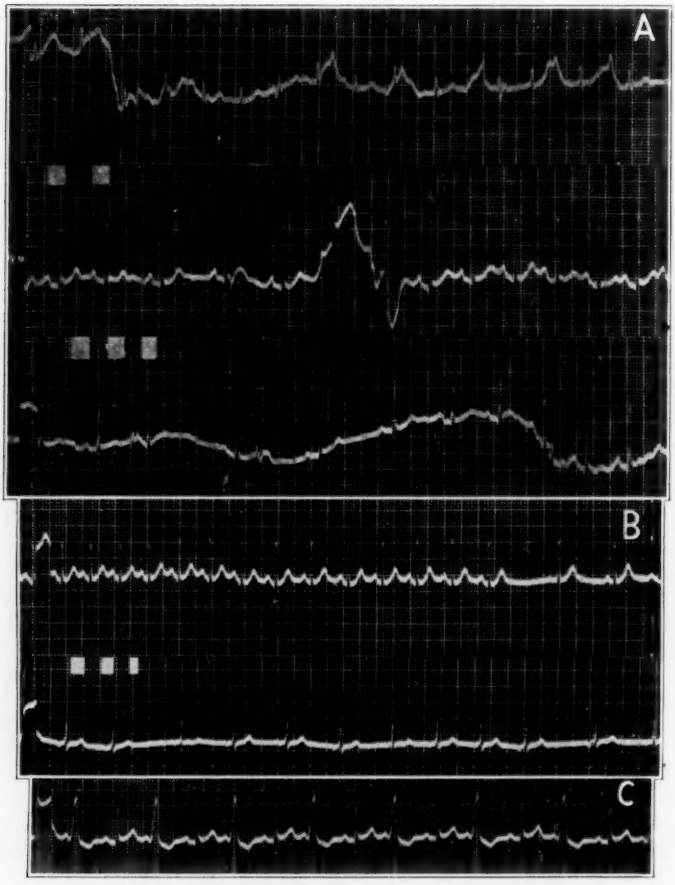


Fig. 3.—*A*, J. C., arrhythmia, with premature auricular and ventricular contractions and probable sinuauricular block; forty-third treatment, stage 3; 80 units of insulin, blood sugar 6 mg. per hundred cubic centimeters, temperature 98.4 F. *B*, C. A., auricular premature contractions, auricular tachycardia; twenty-seventh treatment, stage 3; 60 units of insulin, blood sugar 24 mg. per hundred cubic centimeters, temperature 98.2 F. *C*, L. M., ventricular premature contractions with bigeminal rhythm; eighty-sixth day, 150 units of protamine zinc insulin; blood sugar 44 mg. per hundred cubic centimeters, temperature 98.8 F.

Disturbance in auriculoventricular conduction was not found in this series except with auricular flutter (fig. 2). PR intervals were occasionally apparently shortened (fig. 4). Intraventricular conduction in normal auriculoventricular rhythm was never observed to be definitely disturbed, in spite of marked changes in the QRS patterns.

The patients receiving protamine zinc insulin showed most of the changes described for patients with regular insulin shock therapy. Of importance are the facts that hypoglycemia was usually not nearly so marked in this group and that neurologic symptoms and coma were practically never present at the time tracings were made.

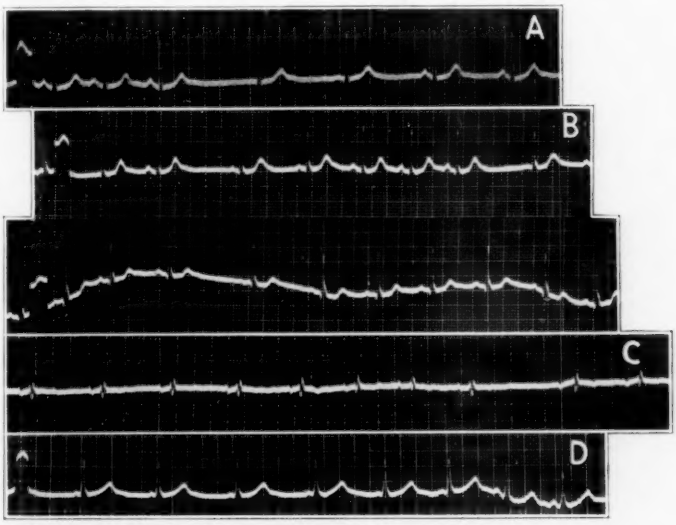


Fig. 4.—*A*, J. M., apparent ventricular escape from sinuauricular block; twenty-third treatment, stage 3; 65 units of insulin, blood sugar 9 mg. per hundred cubic centimeters, temperature 98.4 F. *B*, H. W., multiple recurring auricular foci, with occasional ventricular escape; twenty-first treatment, stage 3; 35 units of insulin, blood sugar 10 mg. per hundred cubic centimeters, temperature 96.4 F. *C*, C. B., before sixty-fifth treatment. Note variability of P wave in lead III, indicating probable multiple auricular foci. Blood sugar 69 mg. per hundred cubic centimeters, temperature 98.6 F. *D*, M. E. M., fifty-third treatment, stage 3; 120 units of insulin, blood sugar 18 mg. per hundred cubic centimeters, temperature 97.4 F. Shortened PR interval, 0.08 second.

Changes in the P waves were varied and frequent but were not noted in every case. Increased P waves in leads II and III, as described by Hadorn, have been observed (fig. 5 *A* and *B*). Inversion and notching of P waves were not infrequent, and when observed they were usually

in leads II, III and IV. The change in the form of the P waves is likely to be progressive and persistent through the course of the treatment. This holds true also for the other changes in wave form about to be described.

Remarkable and striking changes were observed in the QRS complexes in all leads, but the complexes were most widely divergent from

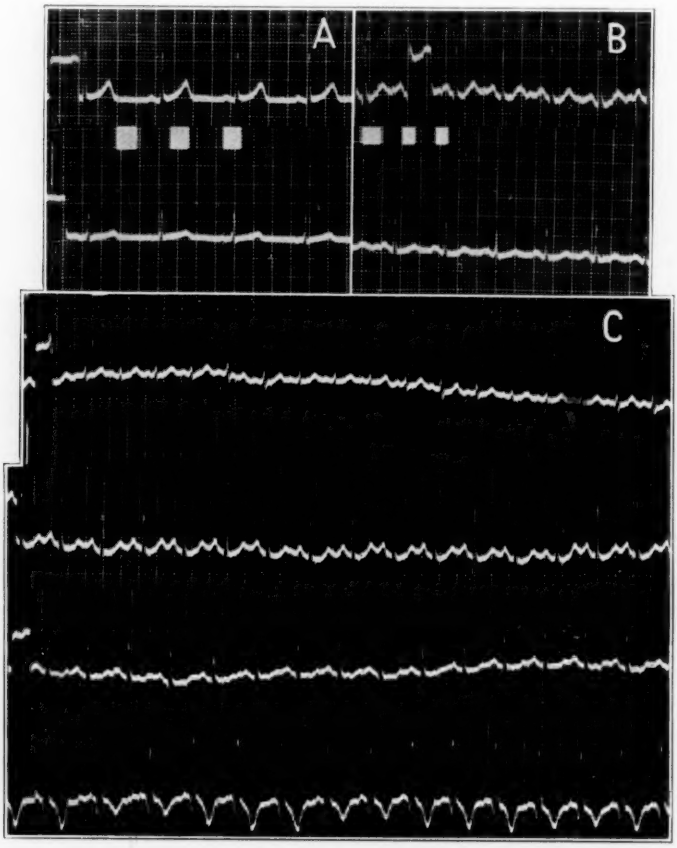


Fig. 5.—*A*, C. A., before fifty-seventh treatment; blood sugar 75 mg. per hundred cubic centimeters, temperature 99.3 F. *B*, C. A., fifty-seventh treatment, stage 3; 75 units of insulin, blood sugar 8 mg. per hundred cubic centimeters, temperature 98 F. Tracing B taken at fastigium of shock, with marked tonic spasms. Note increase in P wave in leads II and III from original level. *C*, B. D., forty-first treatment, stage 3; 170 units of insulin, blood sugar 19 mg. per hundred cubic centimeters, temperature 94.4 F. Note marked alternation in all leads.

the normal in lead III and in the chest lead. Occasionally moderate increase in voltage in leads I and II was seen during the depth of insulin shock. The most regularly observed change was diminution in voltage or even reversal to negativity of the main deflection. This was most marked at the time of deepest shock, but the effect was cumulative through the series of treatments and in many instances was evident a

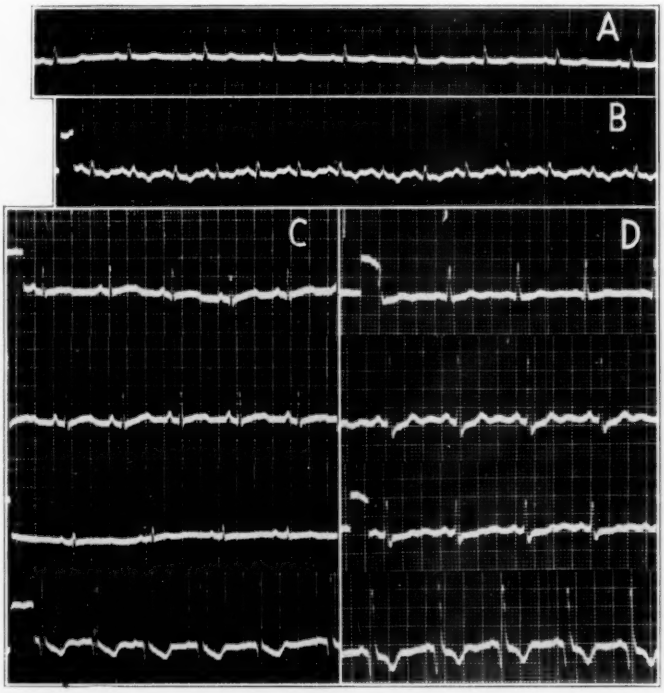


Fig. 6.—*A*, B. D., control tracing before treatment. *B*, B. D., ninth treatment, stage 3; 200 units of insulin, blood sugar 10.9 mg. per hundred cubic centimeters, temperature 95.6 F. Note fragmentation of QRS in lead III. *C*, M. R., before sixty-third treatment; blood sugar 81 mg. per hundred cubic centimeters, temperature 98 F. Note elevated ST segment in leads I and II. *D*, A. S., twenty-first treatment, stage 3; 50 units of insulin, blood sugar 12.5 mg. per hundred cubic centimeters, temperature 95.2 F. Note U wave and marked alternation in leads II and III.

month or more after the final treatment. More significant, perhaps, than the change in voltage was the occurrence of marked "phasic" fluctuation in voltage. This was noted in all leads at one time or another

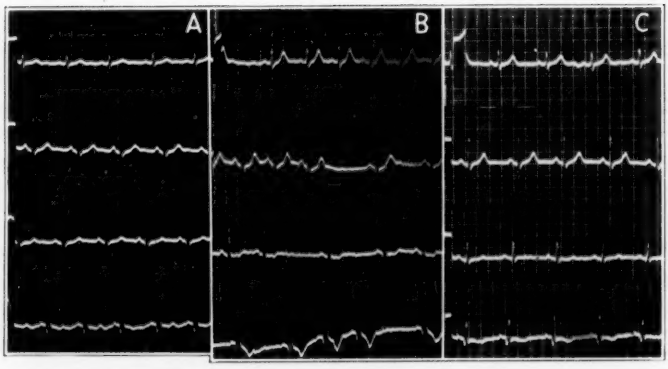


Fig. 7.—Electrocardiograms of J. M. *A*, control tracing before treatment. *B*, fortieth treatment, stage 3; 75 units of insulin, blood sugar 11 mg. per hundred cubic centimeters. Note marked change in T waves in leads III and IV and abnormality of rhythm, probably of supra-auricular origin. *C*, six weeks after discontinuing insulin treatment. Note change in T wave still evident in leads III and IV.

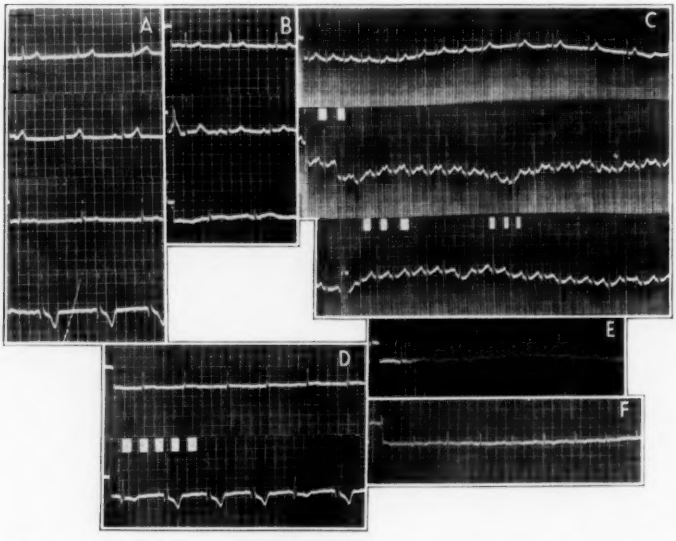


Fig. 8.—Electrocardiograms of J. C. *A*, before first injection of insulin, with blood sugar 83 mg. per hundred cubic centimeters. Note slight abnormality of ST segments in leads II and III. *B*, after first injection of insulin (20 units), no coma; blood sugar 29 mg. per hundred cubic centimeters. T waves in leads I, II and III are definitely depressed. *C*, twenty-ninth treatment, stage 3; 90 units of insulin, blood sugar 12 mg. per hundred cubic centimeters. Note auricular arrhythmia with and without marked tachycardia. *D*, before forty-third treatment; blood sugar 81 mg. per hundred cubic centimeters. Note elevation in ST segment and marked irregular alternation in chest lead. The T wave in lead III is practically isoelectric. *E*, control tracing ten days after discontinuing treatment. Note persistence of the inverted T wave in lead III. *F*, control tracing taken six months after discontinuing treatment. The T wave in lead III remains inverted.

but again was most striking in lead III, where the main deflection may vary from positive to negative within a few beats (fig. 5 *C*). It seems impossible that this fluctuation should indicate grave physiologic disturbance in the myocardium, since it reflects no clinical symptoms. Shift of the electric axis with respiratory phase is the probable explanation for this phenomenon.

Besides change in voltage, the QRS deflections underwent marked metamorphosis during the weeks of treatment. Fragmentation of originally normal complexes with production of "w" complexes and other bizarre forms was frequent. Prominent Q and S deflections occurred, but with no regularity (fig. 6 *A* and *B*).

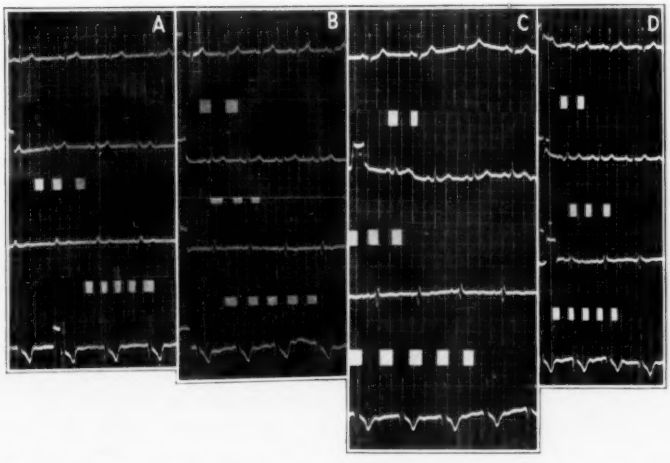


Fig. 9.—Electrocardiograms of C. B. *A*, control tracing before first injection of insulin. Note the "W" form of the QRS segment in lead III. *B*, before ninety-first treatment; blood sugar 65 mg. per hundred cubic centimeters. Note inversion of the T wave in lead III. Note the U wave in the chest lead. *C*, ninety-first treatment, stage 3; 150 units of insulin, blood sugar 12 mg. per hundred cubic centimeters. Note marked alternation in lead III, with respiratory rhythm. The T wave in lead III is isoelectric or diphasic. *D*, control tracing six weeks after discontinuing treatment. Note that the T wave in lead III is still inverted and that the QRS segment in lead III has not yet returned to its original form.

ST intervals and T waves showed marked changes from the normal during hypoglycemia, with progressive cumulative deviation through the course of the treatment. Elevation or depression of the ST interval was most frequent in leads II and III (fig. 6 *C*). Depression and inversion of the T wave was the most characteristic change observed in practically every patient under the influence of insulin, and it persisted, after it was

well established by repeated shock periods, even after rest days. The return to normal often takes several months, according to the present observations, in spite of the opinion of previous authors that the inverted T wave of insulin shock is quickly reversible after termination of hypoglycemia (figs. 7, 8, 9 and 10).

A common observation in hypoglycemia was the "u" wave (fig. 6 *D*), which was of varying depth and was found in any lead, particularly in lead III and the chest lead. The addition of this undulation to the electrocardiogram is unexplained, but it is noteworthy that it was one of the striking and persistent effects of hypoglycemia in many cases.

Prolongation of the duration of systole (after correction for the heart rate) was noted at times. This was determined by calculation according to one of several available formulas after measurement of the "QT"

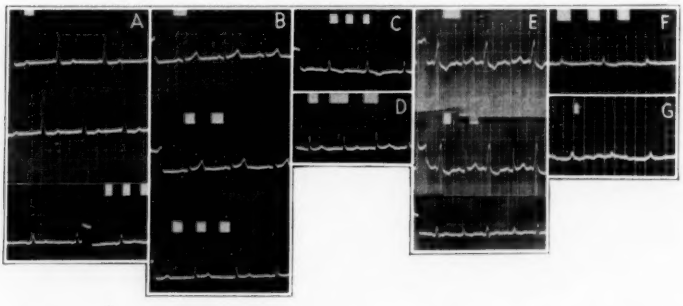


Fig. 10.—Electrocardiograms of L. M. *A*, control tracing before treatment. Note abnormalities of the QRS segment in lead III and the depressed ST segment in leads I and II. *B*, sixth day of treatment; 75 units of protamine zinc insulin daily. Before insulin and fasting in the morning: blood sugar 82 mg. per hundred cubic centimeters. This tracing has a more normal appearance than the control, but note the elevation of the ST segment in leads I, II and III. *C*, thirty-fourth day of treatment; 125 units of protamine zinc insulin; fasting blood sugar 56 mg. per hundred cubic centimeters. The T wave in lead III is inverted. *D*, forty-fifth day of treatment; 125 units of protamine zinc insulin; blood sugar 131 mg. per hundred cubic centimeters after noon meal. The T wave in lead III is upright, and there is definite elevation of the ST segment in lead III. *E*, eighty-sixth day of treatment; 150 units of insulin; blood sugar 44 mg. per hundred cubic centimenters after noon meal. The T wave in lead III is inverted, with normal beats; upright with premature ventricular contractions ("coupled" with normal beats, evident in all leads.). Note "fragmentation" of the QRS segment in lead III. *F*, control tracing after discontinuing treatment three days. The T wave in lead III is still inverted and the QRS segment is fragmented. *G*, control tracing four months after discontinuing treatment. The QRS segment in lead III is still fragmented; the T wave in lead III is isoelectric.

time. The formula of Bazett [8] is most commonly used in the American and English literature: systole $= K \sqrt{\text{cycle}}$. The relative duration of systole is indicated by the value of K. The changes in 2 cases are indicated in table 2. Definite prolongation of the period of systolic contraction is not present in every case during insulin hypoglycemia but is sufficiently frequent to indicate that it is a frequent characteristic of the electrocardiogram during hypoglycemia therapy. This was noted also by Hadorn.

TABLE 2.—*Effect of Insulin on Duration of Systole* ($K = \frac{\text{Systole}}{\sqrt{\text{cycle}}}$. *The Duration of the Systole and the Total Cycle is Determined in Seconds*)

Patient	Date	Duration of Systole, in Seconds: Before Insulin	Duration of Systole, in Seconds: During "Shock"	Insulin, in Units
J. C.	June 3	0.38	....	Control
	7	0.40	....	15
	8	0.40	0.44	25
	14	0.37	0.59	120 (no coma)
	25	0.42	0.40	150 (no coma)
	July 3	0.41	0.39	70
	16	0.415	0.42	90
	31	0.40	0.43	80
	Aug. 15	0.44	0.38	110
	Sept. 3	0.40	....	Control
	Oct. 18	0.41	....	Control
	Feb. 24	0.41	....	Control
M. E. M.	July 5	0.41	....	Control
	16	0.45	0.58	130
	31	0.44	0.43	85
	Aug. 16	0.46	0.47	75
	30	0.45	0.57	140
	Sept. 11	0.46	0.61	120
	21	0.42	....	Control
	Oct. 17	0.45	....	Control

COMMENT

The changes in the electrocardiogram resulting from insulin hypoglycemia are not merely daily recurring deviations from a constant normal pattern but are progressive and cumulative from day to day and only slowly recede to the control level after cessation of treatment. Several abstracted series of tracings are illustrated (figs. 7, 8, 9 and 10). It is evident that changes in the various waves are produced by small doses of insulin in some instances, but in the early stages of the treatment the changes disappear to a great extent by the next morning. As the series of repeated hypoglycemic shocks progresses, however, the

8. Bazett, H. C.: An Analysis of the Time Relation of Electrocardiographs, Heart **7**:353, 1920.

changes become less reversible. Both the tracings before the individual shock period and those at the fastigium of hypoglycemia show marked deviation from the control levels. The tracing taken during the period of deepest hypoglycemia shows changes over and above those at the preliminary level, as might be expected, but after each treatment the pattern does not quite revert to the pretreatment level. Return of the electrocardiographic pattern to the appearance previous to treatment is most often slow. Some changes may be evident as long as six months after cessation of treatment (fig. 8). No clinical evidence of change in the myocardium could be determined in any of the patients treated in my series, which now exceeds 200 cases. No congestive or anginal symptoms have been evident, and no changes in the sounds have been observed.

The mechanism of the electrocardiographic changes is only vaguely suggested by the studies here recorded. The questions that arise are: 1. What changes represent response to alteration in the mechanical conditions faced by the heart? 2. What changes represent fundamental physicochemical alterations in myocardial contraction?

The possible changes in circulatory mechanics that take place during insulin shock are limited. A moderate rise in systolic and diastolic pressure is common (table 1), but this is hardly to be held accountable for the electrocardiographic changes. Tonic muscle spasms involving all the somatic musculature intermittently may at times offer some hindrance to the venous return from respiratory obstruction with increased intrathoracic pressure. Increased blood flow in the arms has been shown.[9]

Intermediate between purely mechanical and purely chemical changes in heart action is the effect of asphyxia. This condition can play but a small part in the electrocardiographic changes, for actual asphyxia takes place in hypoglycemic shock only during epileptiform seizures, which are not so common that they can be considered a source of frequent electrocardiographic changes.[10] No distinction in tracings was noted between the patients in this series who had and those who did not have epileptiform seizures. Certainly changes in the tracings of patients who were treated with huge doses of protamine zinc insulin and practically never became comatose cannot be ascribed to any mechanical impedence to heart action or to asphyxia.

Whether insulin itself, the consequent hypoglycemia or perhaps some factor brought out in reaction to these is responsible for the electrocardiographic changes has been a controversial point since electrocardio-

9. Abramson, D. I.; Schkloven, N.; Margolis, M. N., and Mirsky, I. A.: Influence of Massive Doses of Insulin on Peripheral Blood Flow in Man, Am. J. Physiol. **128**:124, 1939.

10. Goldman, D.: Epileptiform Seizures in Insulin Shock Therapy, J. Nerv. & Ment. Dis. **90**:765, 1939.

graphic changes resulting from insulin therapy were first recognized. Reactive epinephrinemia has been hypothesized, and certain work [11] indicates that it actually occurs. Without attempting to settle the questions involved with any finality the following evidence is to be considered. Large doses of protamine zinc insulin with only moderate hypoglycemia cause marked electrocardiographic changes, hardly less than the changes evident during deep hypoglycemic shock. Small doses of insulin can produce changes as abnormal as those produced by large doses. Finally, after cessation of all treatment the electrocardiographic changes recede only over a period of weeks or months, in spite of the absence of any hypoglycemia or excessive measurable insulin physiologically available. Depression or inversion of the T wave often, though not always, seems to be a function of lowered blood sugar.[5] Figure 10 shows, for a patient who was given protamine zinc insulin, an upright T wave in lead III, associated with normal blood sugar, while tracings taken before and after this show an inverted T wave in lead III, associated with low blood sugar.

Probably an important factor in the electrocardiographic changes is the deviation of carbohydrate oxidation brought on by excessive insulin or by the absence of available carbohydrate or by both. That marked muscular exertion can be maintained under such conditions (tonic spasms or epileptiform seizures) has important metabolic implications. Indeed, increased oxygen (O_2) content of venous blood has been observed during hypoglycemic shock by various investigators,[12] presumably indicating reduced oxygen consumption.

It is possible that a variety of glycolytic, "anaerobic" activity is substituted for the usual oxidation mechanisms. A fundamental change in the chemical dynamics of myocardial activity such as this could be expected to show itself in altered electrical manifestations. Further investigation in this direction seems definitely indicated. The earlier investigations of the effect of insulin in perfused hearts, such as the experiments of Hepburn and Latchford,[13] throw little light on the possibilities, although the marked increase in sugar consumption noted by these authors after addition of insulin to the perfusion fluid is undoubtedly in some way significant.

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11. Tietz, E. B.; Dornheggen, H., and Goldman, D.: Blood Adrenalin Levels During Insulin Shock Treatments for Schizophrenia, Endocrinology **26**:641, 1940.

12. Gellhorn, E.: The Action of Hypoglycemia on the Central Nervous System and the Problem of Schizophrenia from the Physiologic Point of View, J. A. M. A. **110**:1433 (April 30) 1938. Himwich, H. E., and Fazekas, J. F.: The Effect of Hypoglycemia on the Metabolism of the Brain, Endocrinology **21**:800, 1937.

13. Hepburn, J., and Latchford, L. K.: Effect of Insulin on the Sugar Consumption of the Isolated Surviving Rabbit Heart, Am. J. Physiol. **62**:177, 1922.

The effects observed in this and in other investigations of the effect of insulin on the electrocardiogram are in some respects similar to those noted in cases of vitamin B deficiency,[14] alkalosis [15] and adrenalinemia.[16] It is reasonable to believe that a common factor in such electrocardiographic changes is a distortion of the normal chemical dynamics of myocardial contraction.

SUMMARY

The electrocardiographic changes associated with the new insulin shock therapy are described in some detail.

The changes produced are persistent for a time even after cessation of the treatment, but they are not permanent.

No clinical cardiologic changes of significance are produced in the patients.

Changes in the chemical dynamics of myocardial contraction are suggested as the probable cause of the electrocardiographic changes.

14. Dustin, C. C.; Weyler, H., and Roberts, C. P.: Electrocardiographic Changes in Vitamin B Deficiency, New England J. Med. **220**:15, 1939.

15. Barker, P. S.; Shrader, E. L., and Ronzoni, E.: The Effects of Alkalosis and of Acidosis upon the Human Electrocardiogram, Am. Heart J. **17**:169, 1938.

16. Milles, G., and Smith, P. W.: Effects of Epinephrine on the Heart, Am. Heart J. **14**:198, 1937.

DERMATOMYOSITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

I. A CLINICAL REPORT OF "TRANSITIONAL" CASES, WITH A CONSIDERATION OF LEAD AS A POSSIBLE ETIOLOGIC FACTOR

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During the past few years there has sprung up an abundant literature devoted to the subject of dermatomyositis. Despite this, it is commonly believed that this condition is extremely rare. Early in the course of my studies on lupus erythematosus [1] it became apparent to me that there were resemblances between that disease and dermatomyositis. The belief that this was so was based on observations made in cases showing certain similarities in eruption, clinical course, general outcome and especially the occurrence of what seemed to be "transitional" conditions. Contrariwise, there were also encountered many features that appeared to provide fundamental points of distinction, particularly if one considered only typical examples of each disease. In following the courses in such cases it was not uncommon to find that the nature of the clinical picture was often variously interpreted by the dermatologist, internist, pediatrician, neurologist and even the orthopedist. This is also demonstrated in the literature, which has become complicated by the recording of examples of these diseases or manifestations of them under a plenitude of titles. In addition, there are many reported cases in which the original diagnosis was later supplanted by another one, owing to changes in the conceptions held by the individual observer or to the appearance of additional, and apparently different, clinical features. A critical review of the older literature on this and related subjects shows clearly that there is need for a reevaluation of much data that have played a notable part in the formulation of some of the present accepted beliefs.

1. Keil, H.: (*a*) Relationship Between Lupus Erythematosus and Tuberculosis: A Critical Review Based on Observations at Necropsy, Arch. Dermat. & Syph. **28**:765 (Dec.) 1933; (*b*) Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, ibid. **36**:729 (Oct.) 1937; (*c*) Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, Brit. J. Dermat. **49**:221, 1937; (*d*) The So-Called Libman-Sacks Syndrome, Arch. Dermat. & Syph. **34**:124 (Jan.) 1936; (*e*) Tuberculous Skin Lesions, New England J. Med. **218**:783, 1938.

In this paper, however, it will be my principal purpose to record in detail several unusual cases illustrating "transitional" conditions, together with the results of a personal follow-up study of a number of instances already described or mentioned briefly in the literature. These protocols were selected to depict the manifold phases of this group of anomalies, and additional examples will be mentioned only as they bear on the elaboration of certain points.

REPORT OF CASE 1

The patient was observed on many occasions by a number of dermatologists, who, though recognizing the peculiarities in the clinical course of his condition, were unable to agree on a definite diagnosis. The disease presented by him was first described on May 18, 1931, at a meeting of the Brooklyn Dermatological Society, as a possible example of porokeratosis (?).[2] At this time the patient was 19 years old, a pressman, and complained of a rash of one year's duration. There was a reddish and violaceous eruption from the tips of the fingers to the wrists. Over the metacarpal and phalangeal joints there were ovoid, well defined, glistening patches characterized by exaggeration of the cutaneous lines (?) as well as by dry, hard, adherent scales and slightly infiltrated borders. The palmar surfaces of the fingers and the skin over the elbows revealed lesions similar to those just described but irregular in shape and redder. A few pinhead scars were observed on the palms. The clinical appearance seemed not to bear out the usual description of porokeratosis, and the diagnosis was based on a biopsy report, which read as follows: "The section showed a persistence of the elastic tissue. The hematoxylin stain showed an epidermis that was acanthotic, with several horny plugs at the follicle openings. There was a peculiar lamellation of the horny layer which was very much thickened. Blood vessels were dilated and surrounded by moderate cellular exudate. The diagnosis was porokeratosis." Roentgenograms of the hands disclosed no abnormal changes in the bones. Notwithstanding the histologic report, most of the observers present regarded the condition as one of acute disseminated lupus erythematosus. The interesting points recorded in the discussion were that the atrophic areas over the elbows were analogous to those observed in acrodermatitis chronica atrophicans or epidermolysis bullosa (Chargin); that there were lesions in the oral mucous membranes (Abramowitz), and that there was atrophy of the thenar eminences (Lyons). The occurrence of a systemic reaction was noted by one of the men, who remarked that the patient seemed to be ill.

Several months later the patient was examined again. The history obtained at this time was of great interest. At the age of 10 years he had an attack of scarlet fever accompanied by sinusitis (right antrum). From the age of 14 years he passed urine once nightly. Two years before the present observation he began to work in a printer's shop. He enjoyed good health until five months later when, after handling lead material, printer's ink and other chemicals, he noticed an erythematous rash over the hands, wrists and elbows; it was most marked over the tips of the fingers, which were extremely tender, a circumstance attributed to the local use of "cre-solvent." A group of observers were led, on the basis of this history, to regard the condition as one of dermatitis venenata, possibly due to printer's ink. The patient began to lose weight gradually. About eight months

2. Berkowitz, B. B.: Case of Porokeratosis? Arch. Dermat. & Syph. **24**: 1124 (Dec.) 1931.

before the present observation, the rash over the elbows became more conspicuous, and fresh lesions appeared on the face. The eruption on the hands faded slowly until it attained its present state. It was difficult for the patient to make a fist, and he complained of pains about the knuckles, wrists and knees. He also noticed thinning of the musculature of the hands. There were no peripheral palsies or wrist drop. He suffered from palpitation and dyspnea on exertion.

On examination the patient did not appear to be acutely ill. There was a generalized eruption showing the following attributes: On the cheeks and nose there was a faint and diffuse erythematous lesion, slightly scaly, spread in a "butterfly" configuration over the "flush area" and accompanied by a light brownish pigmentation (fig. 1). Atrophy was absent. The margins of the ears showed

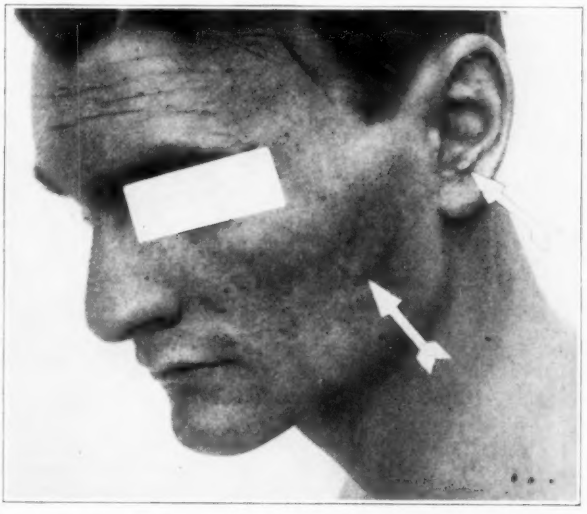

Fig. 1 (case 1).—Erythematous lesions in a case of dermatomyositis. One arrow points to a lesion on the ear; the other to an area of light brown pigmentation in "butterfly" configuration.

pea-sized, erythematous, atrophic areas covered with dry, adherent scales (fig. 1). The external aspects of the regions of the elbows were sites of large, bluish red, atrophic patches, smooth and somewhat scaly, resembling those associated with acrodermatitis chronica atrophicans or the healed stage of epidermolysis bullosa (fig. 2). The palms and especially the fingers showed superficial, small, erythematous lesions, marked by adherent scales and atrophy in some areas. Noteworthy were the smooth, atrophic, shiny patches over the knuckles (fig. 3); these revealed fine telangiectatic vessels over the surface. On the hard palate and the dorsum of the tongue there were a few small, red lesions, superficially denuded and with telangiectasia in occasional areas. The scalp and nails were not affected.

Examination of the heart revealed a snapping first sound at the apex; the second pulmonic sound was louder than the second aortic sound. The temperature was 99 F. and the pulse rate 110. Lymph nodes the size of a hazelnut were

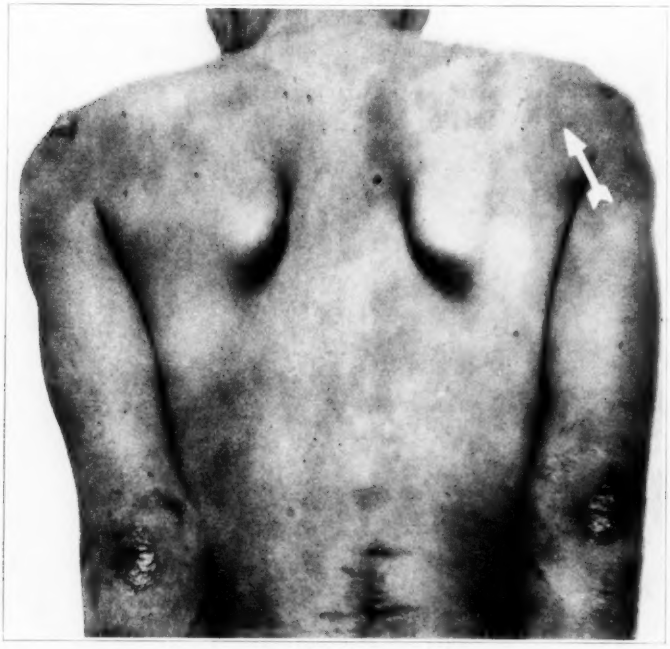

Fig. 2 (case 1).—Lesions over the regions of the elbows. The arrow points to atrophy of the muscles of the shoulder girdle.

Fig. 3 (case 1).—Patches over the small joints of the hands. The arrow points to a characteristic lesion over one of the metacarpophalangeal joints. Atrophy of the interosseous muscles can be seen.

palpated in both axillas. The tip of the spleen could be felt on deep inspiration. The interosseous muscles and the thenar and hypothenar eminences were markedly wasted; however, there was no reaction of degeneration, stimulation with the electric current giving results within the range of normal. A blood culture was sterile for ordinary bacteria and for the tubercle bacillus. A specimen of stool showed no blood. The hemoglobin content was 76 per cent; the white blood cell count was 4,900, with 44 per cent lymphocytes. The blood pressure was 120 systolic and 48 diastolic. The temperature curve was subfebrile, a remarkable feature being the patient's unawareness of his fever. At one time it was believed that there was a short presystolic rumble at the apex of the heart, accompanied by some accentuation of the second pulmonic sound. These findings considered in conjunction with a snapping first sound at the apex, splenomegaly, lymphadenopathy, leukopenia and fever, were deemed suggestive of the Libman-Sacks group.

About two weeks after the initial observation, the patient complained of vagrant articular pains, but there was no demonstrable gross evidence of disease in the articulations. A few small, whitish patches, nonulcerated and slightly elevated, were observed in the buccal mucosa. The Pirquet and Mantoux tests were negative. There were moderately diffuse erythematous swellings of both upper eyelids. About a week later the patient had an attack of pallor in the distal phalanges of the fingers, which simulated the asphyxial stage of Raynaud's disease; pressure on the affected parts left bloodless areas for an abnormally long time. It was now learned that he had suffered several such attacks during the antecedent few months. Examination of several urinary specimens revealed no abnormal findings beyond the occasional presence of a few white blood cells. There was no evidence of renal impairment, the urea nitrogen content of the blood being 12 mg. per hundred cubic centimeters and the concentrating power of the urine being normal. The blood calcium content was diminished, the values ranging between 8 and 9 mg. A roentgenogram of the chest disclosed no abnormalities. An electrocardiogram revealed only slight left axis deviation. A specimen of skin from one of the lesions on the knuckles showed, on microscopic study, marked hyperkeratosis, some edema and vacuole formation in scattered areas of the basal layer of the epidermis, as well as dilated blood vessels in the papillary bodies, and an infiltration of round cells about the blood vessels and in the adjacent parts. Sections were not stained for elastic tissue. Histologic examination of an axillary gland disclosed a nonspecific hyperplastic lymph node. Chemical examination of urine showed the qualitative presence of lead by a method in which positive results were considered to indicate abnormal amounts of the metal; another such analysis made two months later was also positive. At no time had there been noted stippling of the red blood cells or other classic evidence of lead intoxication.

During the following two years the disease continued to run a subfebrile course, though the patient remained unaware of the fever. He complained of generalized weakness, and there had been a loss of over 50 pounds (22.7 Kg.) in weight. There was bilateral atrophy of the muscles of the shoulder girdle, the course of this condition being progressive. On several occasions there occurred a widespread purpura of the skin and the oral mucosa, associated with peculiar necrotic, slowly healing lesions on the legs and shoulders. Platelet counts revealed no abnormal changes. The other cutaneous patches remained unchanged, except that the flush area of the face was slightly more pigmented. The patient's sense of weakness seemed to be intensified by inability to use the hands. About six weeks before death, evidence of a "sclerodermic" process appeared on the face

in the form of bilateral thickenings in the cheeks (edema of the skin and subcutaneous tissues?), rendering mobility of these parts difficult and interfering with smiling. The patient died at home as a result of pneumonia after an eventful course of some three years, during which time a variety of diagnoses had been suggested.

COMMENT ON CASE 1

1. *Cutaneous Features.*—The occurrence of an erythema of the face, which assumed a "butterfly" configuration and which was subsequently replaced by pigmentation, the attributes exhibited by the lesions in the ears and in the oral mucous membranes, as well as the peculiar constitutional symptoms, appeared to be consistent with the clinical diagnosis of systemic lupus erythematosus. The initial impression of dermatitis venenata, based on the history of contact with chemicals, was a reasonable hypothesis, but it failed to take into account the systemic features; in a few other cases coming under my observation the early stages of disseminated lupus erythematosus were likewise attributed to contact with chemicals on the face (women) or on the hands (men). The pathologic alterations seemed to differ from those occurring in the average case of discoid atrophic lupus erythematosus, but the changes could be considered as similar to those observed in cases of the superficial varieties of that disease, notably the types accompanied by systemic reactions.[1b] On the other hand, all the lesions noted were not unlike those encountered in typical examples of dermatomyositis, though in this case the painful, edematous muscular swellings generally observed in the latter condition were lacking. Of special interest was the presence of smooth, atrophic, glistening oval patches over the finger joints; these lesions were declared by Gottron to be characteristic, if not pathognomonic, of dermatomyositis, especially in its chronic stage.[3] In 1931 I observed the appearance of a similar anomaly (case 2) in a patient whose condition was diagnosed as "exanthematic" lupus erythematosus and who also had marked muscular atrophy. Since then, other similar cases have come under my observation. It may be stated, then, that this type of eruption seems to be associated commonly with evidence of disease in the muscles; this subject will receive more detailed consideration in another publication. Finally, it is interesting to note the appearance of the peculiar thickenings in the cheeks observed in this patient a few weeks before death, the attributes of these patches simulating "scleroderma." It is my belief, however, in the absence of substantiating pathologic evidence, that the firmness of these areas was caused by an unusual localization of edematous fluid in the involved parts (subcutaneous, probably also cutaneous), a condition capable of

3. Gottron, H.: Hautveränderungen bei Dermatomyositis, in Comptes-rendus du huitième Congres international de dermatologie et de syphilologie, Copenhagen, 1930, p. 826.

complete restitution to normal. This was demonstrated in case 5 (to be reported later in this paper), in which an almost identical phenomenon was encountered.

2. *Atrophy in the Muscles.*—This feature was probably dependent on "primary" disease in the muscles rather than on initial involvement of nerves. The failure to obtain a reaction of degeneration favored this view, although it appears that too much reliance cannot be placed on responses to the electric current. I have also encountered atrophy of the small muscles of the hands in several examples of typical systemic lupus erythematosus; in these cases the clinical features did not in any way suggest the possibility of dermatomyositis. Of particular interest in case 1 was the subsequent development of atrophy in the muscles of the shoulder girdle, a phenomenon observed far more often in instances of dermatomyositis. It must be stressed, however, that at no time during the course were there painful, edematous swellings involving the musculature. Noteworthy was the marked loss of weight, over 50 pounds (22.7 Kg.) in one year; this feature has been commonly encountered in dermatomyositis.

3. *Miscellaneous Features.*—Additional points of interest in case 1 were: (1) a leukopenia and relative lymphocytosis, which occur more commonly in systemic lupus erythematosus, occasionally in dermatomyositis and sometimes in lead poisoning; (2) a febrile state of which the patient was oblivious; (3) a low content of blood calcium, ranging between 8 and 9 mg., the significance of which is, however, unclear, and (4) enlarged axillary glands, showing on histologic examination only the changes of a nonspecific hyperplastic condition.

4. *Etiologic Considerations.*—Study of the composite clinical picture suggested the possibility of a low grade, chronic, infectious process as the underlying basis of the symptoms; yet no evidence to substantiate this view was forthcoming, and the bacteriologic investigations proved fruitless. On the other hand, the onset of symptoms after the handling of chemicals, particularly lead, might have been justifiably regarded at first as coincidental, especially in the absence of classic evidence of plumbism, such as Burton's line, stippling of the red blood cells, colic, constipation and encephalopathy. Nevertheless, absorption of lead may be freely granted in view of its detection by urinalysis on two occasions two months apart; these findings were regarded as significant owing to the use of a relatively insensitive method for its isolation. In addition, the atrophy in the small muscles of the hands (Duchenne-Aran type) and the subsequent involvement of the muscles of the shoulder girdle might have been considered as suggestive evidence of plumbism. Definite criteria for the differentiation of lead intoxication from lead absorption

have been set down by Aub and his co-workers,[4] but it must be admitted that the subject is still in a state of flux, especially in regard to the incipient, mild and atypical examples of this condition. The part played by idiosyncrasy is well recognized in classic instances of the disease, but little is known about its relation to other variants of the clinical picture. Even authentic cases of lead intoxication may occur in the absence of such features as basophilic stippling and discoloration of the gum line, if not permanently, at least temporarily.[5] I have notes on one undoubted example of lead encephalopathy in which chemical examination of urine failed to reveal the presence of this heavy metal, and there are similar cases recorded in the literature. The interesting observation[6] that a period as long as twenty years may elapse between exposure to the metal and the appearance of symptoms of plumbism can be correlated with the deposition of lead in the bones (probably in the form of tertiary lead phosphate), from which site it may be liberated into the blood stream by a series of propitious circumstances. If, on the one hand, it seems reasonable to believe that this heavy metal may enter the body by devious means and that it cannot be blamed for all the ills flesh is heir to, it seems, on the other hand, equally prudent to inquire into its possible relation to the onset or accentuation of obscure clinical pictures ordinarily not attributed to it. The following discussion will be concerned with certain suggestive evidence indicating (1) that lead may possibly play a part in the production or accentuation of conditions similar to that in case 1 and (2) that this may possibly be caused by a pathologic effect on the smaller blood vessels in the body.

In a remarkable monograph on lead poisoning, Aub and his co-workers[4] summarized critically the evidence on the relation of this heavy metal to vascular disease. These investigators were unable to accept such a relationship, as they felt that no one had satisfactorily established proof of specific lesions in the blood vessels. Nevertheless, there are data pointing toward lead as a vascular poison in susceptible persons, though it seems probable that pathognomonic, or even highly characteristic, pathologic changes are not produced. Zadek[7] stated: "Lead belongs to the few vascular poisons of which the mode of action is known. On the basis of numerous clinical, anatomic and experimental observations in animals, we know that lead attacks the vessels, especially the arterioles and capillaries, causing in time a hypertonic (generalized)

4. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Lead Poisoning, Baltimore, Williams & Wilkins Company, 1926.

5. Linenthal, H.: The Early Diagnosis of Lead Poisoning, J. A. M. A. **62**: 1796 (June 6) 1914.

6. Waterfield, R. L.: A Case of Delaved Lead Poisoning with a Latent Period of Twenty-Four Years, Guy's Hosp. Rep. **81**:374, 1931.

7. Zadek, E.: Zur Klinik der chronischen Bleivergiftungen, Ztschr. f. klin. Med. **116**:241, 1931.

arteriosclerosis." Teleky [8] expressed the opinion that "vascular damage may be and remain the solitary sign of poisoning." Fishberg [9] declared that "preeminent among the exogenous poisons which cause chronic hypertension in man, if indeed, there are any others, is lead," and he attributed this effect to "the vasoconstricting action of the metal on the arteries and, perhaps, the capillaries." According to Fishberg, there appears to be suggestive evidence that lead encephalopathy and colic are caused by vasoconstriction of the cerebral and mesenteric vessels respectively, these transitory episodes being designated as "vascular crises" in the sense of Pal.

There are many conditions, at present classified as clinicopathologic entities, in which the vascular system is alleged to be the principal or predominant site of attack. Among these may be mentioned arteriosclerosis (arteriolosclerosis),[10] malignant nephrosclerosis,[11] periarteritis nodosa,[12] dermatomyositis,[13] systemic lupus erythematosus,[1] Raynaud's syndrome [14] and a few others not pertinent to this discussion. As a rule these conditions may be differentiated from one another by the nature and extent of the pathologic changes, the size of the vessels chiefly affected and clinical pictures that are distinctive in most instances. They are often conveniently classified under the generic heading of "diffuse vascular disease;" this general term may, perhaps, represent an advance in conception, but it gives no hint at cause or the finer clinical differentiations, and its employment in nomenclature must not be allowed to degenerate into a veritable shibboleth. The possible relation of some of these conditions to lead absorption and intoxication will be reviewed in the ensuing paragraphs.

(*a*) Renal Vascular Disease: According to Fishberg,[9] the renal changes attributable to lead are definitely those occurring in the arteriolosclerotic (vascular) kidney. Brogsitter and Wodarz,[10] in 8 cases, and Fishberg,[9] in 2 instances, observed marked hypertrophy in the media of the small renal arteries, among other alterations in the vessels of that organ. The article by the former investigators carries a list of

8. Teleky, cited by Zadek.[7]

9. Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

10. Brogsitter, A. M., and Wodarz, H.: Nierenveränderungen bei Bleivergiftung und Gicht, Deutsches Arch. f. klin. Med. **139**:129, 1922.

11. Volhard, F., and Fahr, K. T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

12. Keil, H.: The Rheumatic Subcutaneous Nodule and Simulating Lesions, Medicine **17**:357, 1938.

13. Fahr, T.: Zur Frage der Polymyositis (Dermatomyositis), Arch. f. Dermat. u. Syph. **130**:1, 1921.

14. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw and Sons, Ltd., 1927.

the earlier recorded observations concerned with this relation. In many instances, also, the changes of arteriolar necrosis have been reported; for example, of the 36 patients with "malignant nephrosclerosis" (so-called combination form) studied by Volhard and Fahr,[11] 4 had worked in the lead industries, and 2 of these had previously shown evidence of plumbism. More imposing are the statistics furnished by Machwitz and Rosenberg;[15] they observed that in a group of 36 patients with malignant nephrosclerosis containing 17 men, 9 of the men were lead workers. No case protocols were furnished by Volhard and Fahr, but in the single instance reported in detail by Machwitz and Rosenberg, the pathologic description of which is given by Löhlein,[16] it is clear that the patient had been suffering from saturnism.

In addition to these changes in the arterioles, vascular alterations have also been noted in smaller blood vessels, including the capillaries of various organs.[17] The changes were chiefly concerned with hyaline degeneration of the parietes, accompanied in some instances by the formation of "hyaline thrombi," the pathogenesis of the latter phenomenon being variously interpreted. In most cases the description was limited to but a solitary organ, but when complete postmortem protocols were available it appears that the changes were more or less generalized in distribution. However, none of the vascular alterations seems to be pathognomonic of lead poisoning, but this conclusion need not negate the view relating to the effect of the metal on the blood vessels, the probable primary site of the disease. The evidence compiled appears to be too suggestive to be summarily dismissed on the ground of coincidence.

(*b*) Dermatomyositis: It is Fahr's[13] belief that in many instances of dermatomyositis the initial, fundamental disturbances are in the blood vessels supplying the affected muscles, the alterations being a variant of "necrotizing arteriolitis," possibly allied to periarteritis nodosa. The fourth case[18] to be described in detail in this paper showed evidence

15. Machwitz, H., and Rosenberg, M.: Zur Klinik der "vaskulären Schrumpfniere" Deutsche med. Wchnschr. **42**:1188, 1916.

16. Löhlein, cited by Machwitz and Rosenberg.[15]

17. (*a*) Gaylor, J.: Zur Histologie der Schrumpfniere nach chronischen Bleivergiftung, Beitr. z. path. Anat. u. z. allg. Path. **2**:476, 1888. (*b*) Mott, F. W.: Examination of the Nervous System in a Case of Chronic Lead Encephalitis, Arch. Neurol. & Psychiat. Path. Lab., London **4**:117, 1909. (*c*) Öller, J. N.: Ueber hyaline Gafässdegeneration als Ursache eine Amblyopia saturnina, Virchows Arch. f. path. Anat. **86**:329, 1881. (*d*) Eichhorst, H.: Beiträge zur Pathologie der Nerven und Muskeln, ibid. **120**:217, 1890. (*e*) Freifeld, H.: Zur Frage der pathologisch-anatomischen Veränderungen bei der Bleivergiftung, ibid. **268**:456, 1928. (*f*) Blackman, S. S., Jr.: The Lesions of Lead Encephalitis in Children, Bull. Johns Hopkins Hosp. **61**:1, 1937. (*g*) Brogsitter and Wodarz.[10]

18. Karelitz, S., and Welt, S. K.: Dermatomyositis, Am. J. Dis. Child. **43**: 1134 (May) 1932.

partially substantiating this view. It is interesting that Fahr regarded lead as one of the possible factors in the production of changes grouped by him in the category of "necrotizing arteriolitis;" this belief was in all likelihood based on his observation of similar vascular alterations associated with malignant nephrosclerosis, which, as stated before, had been encountered by Volhard and Fahr in 4 lead workers.[11]

On the other hand, Schuermann[19] recorded a typical example of dermatomyositis, the cause of which he attributed to the patient's exposure to lead. Perusal of this protocol will reveal a clinical course strikingly similar to that shown by case 1 in my report. In addition to that example there came under my observation, about seven years ago, another case of dermatomyositis that is eminently pertinent to this discussion. The patient in that case was examined some two months after she had been using a hair dye, the chemical composition of which was discovered only after her death. The clinical course was at first regarded as that of dermatitis venenata of the scalp,[20] but subsequently there were superimposed the features of dermatomyositis. The latter diagnosis was confirmed by postmortem examination performed some three months after the onset of the condition. Chemical analysis of the hair dye revealed only lead as the active ingredient. Despite the lack of classic evidence of plumbism, it seems probable that absorption of lead was a factor either in the production or in the accentuation of the illness, which ran an acute course, and this observation assumes greater importance in view of the data already discussed. It may be stated that this is a retrospective conclusion based on the results of a chemical analysis of the hair dye, these findings becoming available only after the death of the patient; it is possible that the ordinary evidence of plumbism was overlooked, though there was moderate secondary anemia.

(*c*) Systemic Lupus Erythematosus: The generalized nature of this disease has been discussed briefly in several other communications,[1] and it is probable that the distribution of dermatomyositis, too, is general. Relative to systemic lupus erythematosus, Ludy and Corson,[21] studying specimens of skin by the spectroscopic method, observed appreciable amounts of lead in the specimens of 15 of 18 patients with systemic lupus erythematosus, the remaining 3 specimens showing faint traces of the heavy metal. In 20 specimens used as control material, the results were essentially negative in 17, while the remaining 3 (examples of vitiligo)

19. Schuermann, H.: Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), Arch. f. Dermat. u. Syph. **178**:414, 1939.

20. This was probably an erroneous belief, as the features from the beginning were those of a case of originally unrecognized dermatomyositis.

21. Ludy, J. B., and Corson, E. F.: Lupus Erythematosus: Increased Incidence, Hematoporphyrinuria and Spectroscopic Findings, Arch. Dermat. & Syph. **37**: 403 (March) 1938.

revealed traces of lead. On the other hand, in 3 cases of lead poisoning spectroscopic examination of specimens of skin gave negative results. These findings are of fundamental interest, though it is difficult to be certain of the interpretation; in any event, substantiation of these data would be desirable before they are utilized generally. Ludy and Corson cited the record of Traub's patient,[22] a painter, as tending to substantiate their findings; it is of great interest, therefore, to report that this reference concerns the patient whose history is now detailed as case 1 in my report.

(*d*) Absorption of Lead by the Skin and Other Cutaneous Phenomena: So far as the lead industries are concerned, absorption of the metal through the skin has been relegated generally to a minor position, if not entirely denied. There is, however, suggestive evidence that this may occur under certain conditions, with the production of symptoms of intoxication. Where the integument has been destroyed or its vitality impaired from any cause, absorption of lead has been freely granted, as in the instances recorded by Pässler (eczema),[23] Gottheil (burn) [24] and Hahn [25] among others. The evidence on the question of absorption of the heavy metal through apparently intact skin is, however, more difficult to assess, in view of the opportunities for lead to gain access through the respiratory tract. There are a few such cases of intoxication, in which the patients used cosmetics containing this ingredient for many years [26] without having a dermatitis, but, as stated, the interpretation of these examples presents insurmountable difficulties; the modern opinion is that lead has been absorbed through the respiratory system. In any event, it is striking that in most cases the etiologic agent was discovered accidentally or only after amazingly long periods of observation.

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22. Traub, E.: A Case for Diagnosis (Lupus Erythematosus Disseminatus?), Arch. Dermat. & Syph. **25**:562 (March) 1932.

23. Pässler, H.: Acute Bleivergiftung bei Ekzem nach Behandlung mit Diachylonsalbe, München. med. Wchnschr. **41**:85, 1894.

24. Gottheil, U. S.: Fatal Lead Poisoning from the Use of Burrow's Solution, J. A. M. A. **54**:1056 (March 26) 1910.

25. Hahn: Encephalopathia saturnina bei einem 13 monatlichen Kinde durch Hebrasalbe: Tod, nebst Bemerkungen über die Eclampsie, Arch. f. Kinderh. **28**: 172, 1900.

26. (*a*) Holland, J. W., in Peterson, F., and Haines, U. S.: A Text-Book of Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1904, vol. 2, p. 385. (*b*) Oliver, T.: Lead Poisoning, New York, Paul B. Hoeber, 1914. (*c*) Robinson, G. W.: Lead Poisoning from the Use of Cosmetics: Two Cases of the Neuromuscular Type, J. A. M. A. **64**:814 (March 6) 1915. (*d*) Sante, L. R.: Lead Neuritis from Cosmetics, with Report of Two Cases, ibid. **64**:1573 (May 8) 1915. (*e*) Woltman, H. W.: Lead Poisoning from Face Enamel, ibid. **79**:1685 (Nov. 11) 1922. (*f*) Barron, M., and Habein, H. C.: Lead Poisoning, with Special Reference to Poisoning from Lead Cosmetics, Am. J. M. Sc. **162**:833, 1921. (*g*) O'Carroll, J.: Saturnine Encephalopathy, Dublin J. M. Sc. **95**:1, 1893.

The symptoms of plumbism have been explained largely on the basis of vasoconstriction of the blood vessels. The pains in the fingers, toes and perhaps also in the joints, which are often encountered in workers in the lead industries, have been attributed to vascular spasms. Similarly, it is possible that spastic constriction of the digital arteries may cause a clinical picture resembling Raynaud's syndrome, and, as this condition nearly always occurs in women, the observation of exceptional cases of its occurrence in men takes on added significance.[27] Among the exogenous poisons causing "symmetric angio-spastic gangrene," Curschmann [28] mentioned lead. It is interesting that Raynaud himself [27a] encountered an instance of the syndrome in a lead worker who also had intermittent amblyopia. Cassirer [27b] observed another instance in a man who had been exposed to the heavy metal and had previously manifested signs of saturnism. The observation of a Raynaud-like syndrome in case 1 in this paper seems interesting in this connection. Sainton's [27c] patient, a painter, had several exacerbations of a condition like that in Raynaud's disease, after resumption of his occupation, and these attacks were accompanied by colic; the process went on eventually to gangrene of the affected parts. Timme's case [27d] was especially noteworthy, as his patient had "obliterative endarteritis." In a subsequent communication, Timme [27e] reported that the left foot of that patient had been amputated, that large amounts of lead were found in the muscle tissue and that "the cross section of one of the arteries showed obliterative arteritis with hypertrophy of the media, together with disappearance

27. (*a*) Raynaud, M.: New Researches on the Nature and Treatment of Local Asphyxia and Symmetrical Gangrene of the Extremities, translated by T. Barlow, in Selected Monographs, London, The New Sydenham Society, 1888. (*b*) Cassirer, R.: Die vasomotorisch-trophischen Neurosen, ed. 2, Berlin, S. Krager, 1912. (*c*) Sainton, H.: Asphyxie symmétrique des extrémités et ménace de gangrène chez un saturnin, France méd. **1**:221, 1881. (*d*) Timme, W.: A Case of Endarteritis Obliterans, Boston M. & S. J. **174**:539, 1916; (*e*) Obliterative Arteritis and Lead Poisoning, Lancet **2**:162, 1916. (*f*) Decloux; Ribadeau-Dumas, and Sabaréanu: Localisations rares de la maladie de Raynaud, Presse méd. **10**:783, 1902. (*g*) Mader: Angioneurosis spastica; Besserung, Jahrb. d. Wien. k. k. Krankenstalten **1**:668, 1892. (*h*) Kazda, F.: Gangrän an den unteren Extremitäten bei Bleiarbeitern, Wien. klin. Wchnschr. **36**:694, 1923. (*i*) Baader, E. W.: Beobachtungen an gewerblichen Bleivergiftungen auf der Abteilung für Berufskranke des Kaiserin Auguste Viktoria Krankenhauses zu Berlin-Lichtenberg, Opera collecta, congressus medicorum internationalis pro artificibus calamitate afflictis aegrotisque Budapest, 1928, p. 411. (*j*) Lederer, E.: Bleigangrän, schwere, bei einem Glass-schleifer, Samml. Vergiftungsfällen **3**:115, 1932. (*k*) Rutishauser, E.: Bleigangrän und Encephalopathie, Virchows Arch. f. path. Anat. **297**:119, 1936.

28. Curschmann, H.: Raynaudsche Krankheit (Symmetrica angiospastische Gangrän), in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1926, vol. 5, pt. 2, p. 1467.

of the media as described by Kolisko."[29] Similar cases have been recorded by a number of other observers[27f,k]; in nearly all of them the attacks occurred during states of chronic plumbism. In 2 unusual instances of disseminated obliterative arteritis recorded by Barker and his co-workers,[30] the factor of lead was regarded by them as coincidental, though in 1 instance there was definite evidence of a previous intercurrent attack of saturnism; yet in the light of the data recorded in this paper it seems wise to reconsider the significance of this factor in relationship to these cases.

On the basis of the data submitted, it seems probable that lead may act on the blood vessels in any of the three following ways, although there need be no specific changes in the pathologic appearance of these structures:

1. It may have a direct action. This presupposes a primary toxic effect on normal blood vessels.

2. It may have an indirect action. Vessels already affected for one reason or another may be further damaged. Patients affected in such a manner need not show the classic evidence of lead poisoning. In this respect the behavior of the heavy metal would be analogous to that of gold salts acting on the previously altered vasculature in cases of systemic lupus erythematosus.[1]

3. Lead may render the blood vessels more prone to damage from still other causes, such as exposure to cold.

In studying this problem further, it must be determined more definitely (*a*) whether lead is indeed a vascular poison under exceptional circumstances, and (*b*) what its mode of action may be on presumably healthy and on previously altered blood vessels.

REPORT OF CASE 2

In 1931 this case was presented before the Frankfurt Dermatologic Congress[31] as an example of "exanthematic" lupus erythematosus. This diagnosis was accepted without demur by a host of competent dermatologists. Prof. O. Gans made it possible for me to observe the patient for over two months. As there were numerous features of unusual interest

29. Kolisko, cited by von Schrötter L.: Erkrankungen der Gefässe, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1901, vol. 15, pt. 3, sect. 2, p. 82.

30. (*a*) Barker, N. W., and Brown, G. E.: Progressive Disseminated Obliterating Arteritis of Unknown Origin, M. Clin. North America **16**:1313, 1933. (*b*) Barker, N. W., and Baker, T. W.: Proliferative Intimitis of Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis, and Recurring Necrotic Ulcers of the Skin, Ann. Int. Med. **9**:1134, 1936.

31. Seier: Lupus erythematodes exanthematicus, Zentralbl. f. Haut- u. Geschlechtskr. **40**:175, 1932.

and as the interpretation of the findings may provoke considerable debate, it seems desirable to outline the clinical aspects from notes taken during the early part of October 1931 and later.

When first seen by me the patient, a girl of 10 years, had already been in the hospital for almost one year. The illness began about November 1930, when there appeared a generalized rash, interpreted as scarlet fever. This was followed by sore throat, a hacking cough and vague pains in the body. At this time there were tense swelling and flaming redness of the left eyelids, accompanied two weeks later by a similar condition of the opposite eye, cheeks and knees, with pains in these parts. About Christmas of 1930, vesicles and bullae appeared on the knees and buttocks; these lesions resembled erythema multiforme exsudativum. There was also a purulent discharge from the eyes, the nature of which remained obscure. At about this time the child was brought for consultation to the clinic of Professor Gans. The brief account by Seier [31] stated that after the healing of bullous lesions, there appeared papular, partly confluent efflorescences showing atrophy and follicular hyperkeratosis; that at one time there was an acute exacerbation of the condition associated with flaming redness and swelling of the entire face, fingers and knees as well as "ulcerations" of the eyelids; that the tuberculin test was negative, and that the clinical picture resembled "sepsis" accompanied by bacterial endocarditis, "polyarthritis," edematous swellings of all the extremities and "polyneuritis." It is, however, only fair to note that there may be disagreement with this interpretation of the clinical features, and I therefore take this opportunity to interpolate additional notes with commentaries on the interpretation of the physical findings and the subsequent course.

The initial examination revealed enlarged inguinal, and a few small nuchal, glands. There was evidence of rhinitis. The mucous membranes were normal. The face was the site of a typical "butterfly" lesion, characterized by erythema, fine, adherent scaling, but no atrophy such as one is accustomed to observe in instances of discoid lupus erythematosus. The ears revealed a few scaling erythematous patches. The skin of the extensor aspects of the knees and elbows showed a symmetric disposition of bullae that had collapsed to form hemorrhagic crusts. There was erythema of the buttocks, with small interspersed areas of fine atrophy. At this point it seems important to stress the localization of erythematous, scaling, definitely atrophic lesions over the joints of the fingers on their dorsal aspects, an appearance recalling the attributes of the patches observed in case 1. In addition, the extremities were sites of acrocyanosis at their peripheries. The articulations showed no evidence of swelling. Physical examination of the heart and lungs revealed no abnormalities at the time. There was moderate secondary anemia and leukopenia on a few occasions. Several platelet counts gave normal figures. Early in the course several examinations of urinary specimens showed red blood cells and casts; the concentrating power of the urine was not determined. The temperature curve was at first high and fluctuating and was later subfebrile. On one occasion frank hematuria appeared, but I subsequently ascertained that this had occurred about three weeks after the institution of therapy by injections of a gold salt. Furthermore, petechiae were observed and a tendency to thrombopenia, but it was difficult to be certain whether this entire transient episode could be attributed to this medication, whether it represented an indirect exacerbation of "systemic lupus erythematosus" owing to superimposed damage to vessels already affected by the principal condition or, finally, whether these phenomena merely represented another manifestation of the disease itself. A roentgenogram of the chest disclosed no evidence of tuberculosis. Several cultures of blood were sterile,

except on one occasion when both a nonhemolytic streptococcus and Staphylococcus aureus were isolated (probable contamination?).

The patient was treated symptomatically with several transfusions of blood, and coincidentally the cutaneous lesions began to fade. An unusual feature, and the reason for the inclusion of the case in this report, was the occurrence of marked progressive atrophy of the muscles in the lower limbs, rendering movement of these parts difficult, if not impossible. The consulting neurologist attributed the condition to "septic polyneuritis," and a favorable prognosis was given. I was unable to agree with this opinion for reasons to be detailed under the general discussion of this case. The wasting of the muscles was apparently preceded by a stage of slightly painful edematous swellings of all the limbs, but the atrophy appeared chiefly in the musculature of the lower extremities, so that the child was unable to stand without the help of an attendant. For the relief of this condition she was placed under the care of an orthopedist. A curious feature was the unusual growth of hair on the forearms, a manifestation which is often mentioned in connection with cases of dermatomyositis and which I have encountered on several occasions.

Subsequently, cardiac murmurs were heard, and the diagnosis of endocarditis was therefore postulated. At this time the urinary sediment was free from formed elements. A tuberculin test was now positive and when repeated gave an even stronger reaction; however, the interpretation of these results remained speculative. At the time of the child's discharge from the hospital toward the end of 1931, the facial erythema was still visible in the form of red scaly lesions, especially over the upper eyelids, with similar symmetric patches over the knees and with peculiar areas of atrophy on the skin overlying the dorsal aspects of the joints in the hands. There were pronounced atrophy of the lower limbs and practically complete loss of power in these parts. The child was sent home, though one could hardly talk of cure, considering the state of the lower extremities. I later learned that the child became worse and was admitted to a hospital in a neighboring town.

COMMENT ON CASE 2

The clinical attributes of the eruption and the nature of the constitutional symptoms (such as fever, urinary findings, lymphadenopathy and exacerbation following injections with a gold salt) were consistent with the diagnosis of "exanthematic" lupus erythematosus, or subacute disseminated lupus erythematosus. The features exhibited by the dermatosis were considered so typical of this disease as to provoke no contrary opinion. Of particular interest were the atrophic patches in the skin overlying the joints of the fingers; these lesions recalled the ones observed in case 1. The most striking feature in the case was the diffuse muscular wasting of the lower extremities, which rendered the child paralytic. The neurologic opinion that this manifestation belonged in the category of "septic polyneuritis" was based on a doubtful interpretation of a single positive culture of blood in the face of several previous sterile results. It is my belief, however, that this condition was an instance of "primary" disease in the muscles of the lower limbs, showing the following characteristics:

1. Diffuse wasting of muscles. This was apparently preceded by a stage of edematous swelling in all the limbs, notably the lower ones.

2. Absence of severe pain. The painful element was not striking at the time of my examination, and there was no evidence that pain had ever occurred in the standard distribution of the suspected nerves.

3. A distribution of diseased muscles not in correspondence with that which one would expect from involvement of nerves alone. Diminution of the deep tendon reflexes is by no means a differentiating feature.

I have encountered subsequently a case of an almost identical condition in a child about 4 or 5 years of age: There were puffiness and swelling about the eyes, a subfebrile course and progressive atrophy and paralysis of the lower limbs. The occurrence of diseased muscle was substantiated by microscopic study of a biopsy specimen, and it was evident that the wasting condition had arisen and progressed in an insidious and painless manner. In this case, also, I noted peculiar erythematous, scaly and somewhat atrophic lesions over the small joints of the hands, a photograph of which will be found in a succeeding publication.

It is reasonably certain that had stimulation with the electric current been carried out in case 2 a reaction of degeneration would have been absent. Neurologists seem hardly to be familiar with this peculiar condition in its various and manifold phases. In addition to the diagnosis of "septic polyneuritis," I have known conditions of this sort to be classified as progressive muscular atrophy, pseudo-hypertrophic muscular dystrophy and, in the end stages, as "scleroderma." Orthopedists are likely to observe these conditions in the chronic phases and to designate them as myositis fibrosa without realizing the relation to the early muscular phenomena occurring in typical instances of dermatomyositis. Several years ago I observed the patient whose condition was described by Blau (case 1 in his report)[32] under the title of myositis fibrosa. In this instance, also, there were the peculiar atrophic lesions over the phalangeal joints, and there was a history of a previous condition that could be readily fitted into the clinical picture of a mild case of dermatomyositis (rash on the arms, a febrile course of several weeks, extreme weakness and persistent dysphagia). This case was originally regarded as one of poliomyelitis, a diagnosis often made in such instances. The contractures about the large, and occasionally the small, joints are also often interpreted by neurologists and internists alike as manifestations of rheumatoid arthritis. Of this syndrome I have encountered several striking examples; in all these cases the significance of the cutaneous manifestations seemed to have been overlooked. These instances are of wide interest, for they shed light on the prognosis of

32. Blau, A.: Primary Generalized Myositis Fibrosa: Report of Two Cases with Histopathology, J. Mt. Sinai Hosp. **5**:432, 1938.

this group of anomalies, but unfortunately the privilege of observing large numbers of these conditions in various phases of development is granted to but few. My own observations indicate strongly that these anomalies are far from rare.

The occurrence of hypertrichosis of the forearms is a feature commonly encountered in cases of dermatomyositis, according to my observations and others recorded in the literature. Its presence has led occasional investigators to suspect an endocrine factor. This possibility cannot be entirely negated, but it is my clinical impression that the increased growth of hair represents an effect of mild inflammatory stimulation caused by an antecedent erythema or by pathologic vascular changes in the subjacent subcutaneous and cutaneous tissues. This type of hypertrichosis seems to occur chiefly in areas in which there has been previous involvement of the blood vessels, of which redness and edema often represent the visible phenomena. Why this should occur in some patients and not in others and why this is not observed as commonly in other inflammatory processes implicating the integument, are questions to which our present knowledge fails to provide absolutely decisive answers. It is therefore a phenomenon worthy of further study.

Here, then, is another case illustrating features commonly observed in instances of both systemic lupus erythematosus and dermatomyositis. Many years ago Orzechowski [33] remarked that the diagnosis in such cases depends largely on who first sees the patient, the dermatologist or the neurologist. Case 2 also illustrates the futility of classifying such conditions as "cured," without an adequate system of follow up, whether it is personal or through the mediation of large clinics, for in this case, at least, I was able to ascertain that the patient had experienced another exacerbation of sufficient severity to warrant hospitalization.

REPORT OF CASE 3

The history of this patient, recorded by Davison [34] in 1929, presents many interesting features. An abstract of the most pertinent ones will be given, together with additional interpolated notes. It will be my purpose to show that the diagnosis could have been made ante mortem had more attention been paid to the peculiar nature of the cutaneous manifestations.

A woman aged 23 was first seen at the Mount Sinai Hospital on Sept. 3, 1925. In 1924 she had an attack of sore throat. Several months later she experienced vague pains in the extremities. According to Davison's detailed account, "the condition was first noticed in March 1925, when she observed three dark brown spots on her forehead and redness of the neck and chest. . . . A few weeks

33. Orzechowski, K.: Disseminierte chronische Myositis und Lupus erythematosis, Arch. f. Dermat. u. Syph. **137**:369, 1921.

34. Davison, C.: Dermatomyositis: A Clinicopathologic Study; Report of a Case with a Complete Necropsy, Arch. Dermat. & Syph. **19**:255 (Feb.) 1929.

later she developed pains in both arms, and her face and feet became swollen (edematous) and painful. She sought the advice of a physician, and examination at the time showed a slight elevation in temperature, blowing systolic murmur at the apex and a rapid heart rate." About seven weeks before the first period of hospitalization, the tonsils were ablated. After this operation there occurred gradual progressive swellings of the legs and face, dyspnea, pains in the jaws and brownish pigmentation of the forehead. The patient complained of palpitation and precordial pain.

Physical examination showed an irregular area of brownish pigmentation on the forehead. There was considerable edema about the eyelids, with bluish discolorations especially evident on the right side. The face was puffy, the swelling being nonpitting. The physical signs heard on examination of the heart were interpreted as indicating chronic rheumatic cardiovascular disease (mitral stenosis and insufficiency); the subsequent postmortem examination showed these findings to be erroneous. The hemoglobin content was 65 per cent and the leukocyte count 6,800, with 64 per cent polymorphonuclears. The leukocyte count could be regarded as indicating relative leukopenia in view of the subfebrile course, the temperature occasionally reaching 100.2 F. Examination of urinary specimens revealed no abnormalities. The content of urea nitrogen was 12.6 mg. The basal metabolic rate ranged between + 30 and + 41; these results were, at least in part, attributed to the fever. The blood pressure was 102 systolic and 62 diastolic. Examination of the eyes showed no local lesion to account for the edematous lids, and the fundi appeared normal. There was no evidence of disease in the sinuses. It was suggested by some that this case might be one of acute lupus erythematosus. Others interpreted the regressing lesions about the eyes as those of a fading phenolphthalein eruption. "During this interval [about six weeks] she developed a stiff neck and was not able to move the head and shoulders in any direction, or raise the arms upward." This so-called "asthenia" was originally reported as of "psychic" origin. So far as other cutaneous manifestations are concerned, the record appears to indicate that they were absent, possibly overlooked.

From this time until her death in the latter part of 1926, the patient visited several institutions, finally reaching the Montefiore Hospital, where the diagnosis was arrived at on the basis of the findings at necropsy. For the remainder of the history and physical findings I am indebted to Davison's excellent report. In December 1925 the patient was admitted to the Presbyterian Hospital, where evidence of pulmonary suppuration was observed, for which bronchoscopy was performed. Finally, owing to a recurrence of the symptoms, she entered the Montefiore Hospital, where the following observations were noted: "Examination showed a white woman, undernourished, lying helplessly in bed; she was unable to sit up, and held the head rigidly with the arms at the sides. The skin of the head, neck, chest and upper arms showed a peculiar brownish pigmentation. There was some edema about the face and feet which did not pit on pressure. . . . The sternocleidomastoid muscles could not be felt, and the head could not be supported alone. There was pain on pressure of the neck. . . . The extremities showed a partial ankylosis of the shoulders and elbow joints with muscular wasting, more marked in the upper extremities. The arms could not be raised above the elbows, and the shoulders could not be raised from the pillow. The muscles of the thigh were weak, and painful on pressure. . . . The electrical reactions showed a normal response in the muscles of the upper extremities. The platysma and sternocleidomastoid muscles did not respond to galvanism or faradism. There were no opening contractions." There was clinical evidence of pulmonary

suppuration, and the presence of this complication probably explained the increased white blood cell count (20,900, with 74 per cent polymorphonuclear leukocytes). The blood pressure was normal. There was no evidence of renal disease, aside from a few granular and hyaline casts in the urinary sediment. Roentgenographic examination of the extremities "disclosed moderately advanced arthritic changes of the right elbow, especially in the articular surface of the olecranon. There was slight periostitis along the upper third of the shaft of the radius. The right shoulder revealed slight arthritic changes and moderate amount of bone atrophy along the upper end of the shaft of the humerus." Throughout the course the fever was remittent.

Postmortem examination disclosed several findings that had not been stressed clinically. "The skin over the face and anterior surface of the neck was tense and smooth with a purple color" [superimposed postmortem lividity?]. The extremities showed slight but definite contractions at the elbow, wrist and interphalangeal joints. The overlying skin was thinned out, smooth and purplish over the fingers. The muscles were strikingly thinned out and pale." The other important findings were: in many muscles various degenerative changes, generally advanced (for example, fibrosis); generalized lymphoid hyperplasia (many lymph nodes enlarged, persistent thymus); bronchiectasis of the lower lobe of the left lung; terminal bronchopneumonia, and "contractures with atrophy of the skin of the extremities, face and neck."

COMMENT ON CASE 3

In this case the early history provides features of interest. The condition was diagnosed as acute disseminated lupus erythematosus, chiefly because there were erythematous swellings about the eyelids. The manner in which the lesions underwent gradual involution with the production of pigmented areas (indicating the previous presence of inflammatory changes) was strikingly illustrated by the diagnosis of "fading phenolphthalein eruption." The detailed history related by Davison [34] indicates clearly that early in the course the patient had noted painful edematous swellings of the face and lower limbs, and it is also clear that evidence of muscular atrophy was observed later in the upper extremities, with partial ankylosis resulting probably from the secondary effects of fibrosis. The reactions to the electric current were consistent with those of "primary muscle disease," rather than with primary involvement of the nerves followed by atrophy of the muscles; the former view seemed all the more reasonable since the tests were done more than a year after the onset of the condition. The postmortem protocol noted certain changes in the skin, which recalled vaguely some of the features occurring in the eruptions in systemic lupus erythematosus and chronic dermatomyositis; the latter diagnosis was particularly likely in view of the changes in the integument overlying the joints of the fingers. The impression that the patient had rheumatic heart disease was not substantiated at necropsy, and it seems desirable to stress the point as these cases are often labeled as instances of rheumatic fever. Finally, the occurrence of generalized enlargement of the internal lymph nodes, which was reported by Davison as an

interesting observation, is a phenomenon that is commonly encountered in cases of systemic lupus erythematosus. It is likely that the occurrence of this manifestation will be recorded more often, commensurate with increasing interest in this phase of the disease; the occasional occurrence of necrotic areas in the enlarged lymph glands in instances of systemic lupus erythematosus has been often interpreted, on the basis of superficial examination and study, as evidence of a tuberculous source.

REPORT OF CASE 4

The patient whose case was reported in an interesting paper by Karelitz and Welt [18] (1932) presented a number of dermatologic features that merit a more detailed consideration. Early in 1931 I carried on correspondence with the Massachusetts General Hospital, and on June 10, 1931 this institution furnished interesting notes which bear analysis and from which valuable lessons may be learned. In addition to information from these sources there will be appended a number of personal observations to complete the essential data abstracted from the report of Karelitz and Welt.

A girl aged 6 years became ill "about Aug. 4, 1929, when red streaks were noticed under both eyes. The areas of redness lasted one week, then spread lower down the face, crossing the nose and causing a butterfly-shaped erythema. Within two weeks there were marked anorexia and edema under both lower eyelids; the eruption spread over the extensor surfaces of all the extremities, and there were patchy areas on the buttocks. The diagnosis of lupus erythematosus was made, and ultraviolet ray treatment given, without any improvement. On Sept. 26, 1929, after increasing weakness, loss of weight, edema of the face and persistent cutaneous eruptions, the child was admitted to the Massachusetts General Hospital, where the diagnosis of lupus erythematosus was confirmed. A tuberculin test with a dilution of 1:1,000 was negative, and roentgenograms of the chest were suggestive of enlargement of the hilus gland." At this point the observations made in that institution may be introduced. There was a butterfly-shaped area of erythema extending across the nose onto the cheeks; the patch was smooth and slightly raised. There was some edema around the eyes and on the bridge of the nose. The skin about the elbows and on the extensor aspects of the arms had a blotchy, dusky red hue. There were symmetric similar areas on the buttocks as well as on the knees and shins. With the exception of one feature, to be mentioned in the discussion, the eruption was suggestive of acute disseminated lupus erythematosus. A roentgenogram of the chest revealed the following abnormal condition: The hilus shadows were somewhat increased in density, and the larger lung markings were prominent, especially those running in the left upper portion of the chest; findings were consistent with hilus tuberculosis. There was no evidence of parenchymatous involvement of the lung. In the discharge note, dated Oct. 15, 1929, the condition was classified as lupus erythematosus. It was recognized that though the roentgenographic report stated that the picture was consistent with hilus tuberculosis, there was no clinical evidence, and the tuberculin test, with a dilution of 1:1,000, was negative. In view of the tuberculous hypothesis of lupus erythematosus prevalent at the time, care in a sanatorium was advised. Up to this time there had been no symptoms pointing definitely toward involvement of muscles.

On her arrival at home, "the child first complained of being tired and unable to walk." The face showed edematous involvement, which extended over the entire body. "On October 22, the patient began to have a daily temperature of 99 F. in the morning and 101 F. in the afternoon. Gradually she became unable to move and cried with pain on being moved. . . . A diagnosis of acute rheumatic fever was made . . ." and salicylate therapy in large doses was administered. "The condition remained unchanged until about December 1, when her pulse rate suddenly rose from 100 to 120 to 160 to 180. A systolic murmur was heard, and several days later a diastolic murmur became audible. A cardiologist then concurred in the combined diagnosis of lupus erythematosus diffusa and acute rheumatic fever with endocarditis. About December 20 the temperature began to rise to 103 F. daily, despite the large doses of salicylates." On December 29, the patient was seen by Dr. Karelitz in consultation. He observed that at this time "there was a red erythema, butterfly shape, over the face and nose, and irregular over the dorsal aspects of the arms, elbows, wrists, thighs, knees, legs and ankles. The eruption was scaly and itched; it healed under the eyelids, leaving white areas of depigmentation. The edema was firm, indurated and brawny, and in places, doughy. There was no pitting. The child lay immobile, with marked tenderness on pressure or passive motion. She could not move any part of her body, except her face, without pain. . . . Her forehead was deeply pigmented brown . . . the heart was not enlarged; the pulse rate was 140, and there were a soft systolic and a faint diastolic murmur at the apex. . . . The urine was normal and the blood count was normal except for 5 per cent eosinophils. A diagnosis of dermatomyositis was suggested as the only possibility that might explain the entire clinical picture and history.

"The patient was admitted to Mount Sinai Hospital on Jan. 9, 1930, about the beginning of the sixth month of her illness." On examination it was found that the clinical picture had undergone some changes in that "the edema was less marked, some of the cutaneous lesions had improved [leaving residual areas of pigmentation], and the child could move her toes and fingers. Ulcerations in the inguinal folds and over the internal maleoli [previously noted] had healed. . . . The temperature was 101.8 F., the pulse rate 120 and respiration 28." Examination of the heart revealed only a systolic murmur at the apex, which lacked the attribute of transmission. The edge of the spleen was palpated by some observers. I noted enlarged lymph nodes in the axillas, but these did not become more pronounced subsequently. The extremities showed some muscular atrophy. There was considerable hypertrichosis over the forehead and the upper and lower limbs; the patient's mother stated that this feature had become more marked since the inception of illness. Laboratory reports showed that the Wassermann test was negative; that there was moderate secondary anemia (hemoglobin content, 72 per cent); that there was a striking leukopenia of 4,700 white blood cells, with 67 per cent polymorphonuclears and 9 per cent eosinophils; that the urinary specimens, aside from a faint trace of albumin and occasional white blood cells in the sediment, were free from abnormalities; that there was no evident impairment in renal function, the content of urea nitrogen in the blood and the concentrating power of the urine being normal; that the blood pressure was 114 systolic and 70 diastolic; that the Pirquet and Mantoux tests (up to 10 mg. of old tuberculin) were negative; that the specimens of stool showed no ova or parasites to explain the eosinophilia, and that various roentgenographic examinations (including those of the heart, lungs, sinuses and other parts) disclosed no abnormalities. Of interest was the unexplained increase in the amount of blood calcium (12.4 mg.).

The nature of the rash was variously regarded. On one occasion the diagnosis of lupus erythematosus was eliminated owing to lack of definite evidence of atrophy in the lesions. At another time the sudden appearance on the extensor aspects of the ankles and feet of an irregular, blotchy, violaceous eruption, hemorrhagic and nummular, which did not fade on pressure, was regarded simply as telangiectasia; but the formation of definite telangiectatic rings enclosing apparently healthy centers, perhaps slightly depressed (?), produced a decided resemblance to Majocchi's disease (purpura annularis telangiectodes).

"A biopsy of the biceps muscle performed January 16 showed the typical picture of dermatomyositis: atrophy of the skin, edema and fragmentation of the muscle fibers, loss of striation, fatty degeneration, round cell infiltration and perivascular infiltration around the small vessels." It is interesting that the "electrical reactions of the muscles were normal, the cathodal closure being greater than the anodal; there was prompt response to the faradic current."

On January 28 the skin about the eyes showed a pale erythematous discoloration, with superimposed formation of definite telangiectatic vessels. This was followed by similar involvement in the integument overlying the joints of the hands. Subsequently, the facial erythema became more pronounced, assuming again the typical "butterfly" configuration occurring in lupus erythematosus, accompanied by an intensification in the lesions over the upper eyelids and the appearance of an eruption over the upper part of the chest. The dermatosis was designated by another dermatologist as telangiectasia of the cheeks, chest and knuckles. It was also noted that erythematous and telangiectatic lesions would appear on the abdomen at sporadic intervals, and the same anomaly occurred on the dorsal aspects of the hands, notably over the joints; the areas varied in size from that of a pinpoint to that of a finger nail. Finally, about three weeks before death, another observer suggested the diagnosis of lupus erythematosus disseminatus of telangiectatic type; this opinion was based on the presence of dusky red, purplish patches on the face and dorsum of the fingers, the lesions showing slight, fine scaling and small areas of what was interpreted as incipient, though definite, atrophy. The diversity of opinion was explained by the remarkable variations in the appearance of the lesions from time to time.

"The child gradually was able to move her arms enough to feed herself, and when propped up in a sitting position could bend her knees but not abduct or rotate her thighs. . . . The temperature dropped to normal, but fever recurred off and on for one or more days." The patient was treated symptomatically by diverse methods, without striking or apparent benefit. It is of great interest that exposures "to infra-red and ultraviolet rays and to massage at times caused exacerbation of fever. . . . Several decubitus ulcers developed on the back, and some ulcerations in the axillae. These lesions did not heal under the usual treatment, and the patient died [April 13, 1930, or about eight months after the onset of illness] with a terminal bacteremia," the temperature rising to 106.5 F. and a blood culture showing Streptococcus haemolyticus. However, bacteriologic examinations had, prior to this time, been sterile.

"The postmortem diagnosis was dermatomyositis, acute sepsis, enterocolitis, decubitus ulcers, hypostatic congestion of the lungs" and several other conditions. "Two striking features in the pathologic condition were the involvement of the musculature of the blood vessels and the intestinal ulceration." An excellent illustration of the vascular changes, which were limited in distribution, is provided in figure 3 in the report by Karelitz and Welt.

COMMENT ON CASE 4

As the diagnosis of acute disseminated lupus erythematosus was suggested on a score of occasions, it is evident that the early cutaneous lesions showed striking similarities to that condition. The difficulties in differentiating that disease from dermatomyositis were then considerably enhanced, as there was apparently no clinical evidence of involvement of the musculature. It is probable that the initial appearance of an eruption about the eyes, with subsequent spread to the flush area of the face, is a feature pointing toward the diagnosis of dermatomyositis. In the average case of systemic lupus erythematosus the areas of the eyelids, especially the upper ones, are occasionally involved, but this usually occurs as a secondary spread from an intensified process in the cheeks; there are, however, a few exceptions to this rule. The clinical significance of this phenomenon as well as of the cutaneous lesions over the joints of the fingers has been briefly indicated and will be discussed at length in another publication.

It is also interesting that there were exacerbations of fever after the therapeutic application of ultraviolet irradiation, a response that is commonly observed in the average example of systemic lupus erythematosus. That a similar phenomenon is encountered in dermatomyositis is indicated by a steadily growing literature devoted to this phase of the subject. Here it suffices merely to take cognizance of this fundamental behavior. The practical application of the fact immediately suggests itself and needs no further comment.

The normal reactions to the electric current in this case were consistent with the belief that the muscular involvement occurring in dermatomyositis and related states is, in all likelihood, a primary one rather than the secondary result of involvement of the nerves. The latter view has been suggested in connection with cases characterized by much pain and pronounced atrophy of muscular tissue, but it appears that these symptoms may be explained more satisfactorily on the basis of the former hypothesis. The term "primary muscular disease" does not necessarily eliminate the part played by the alterations in the blood vessels, and, indeed, there is evidence indicating that in many cases of dermatomyositis the fundamental process occurs in the vasculature, with secondary implication of the muscular parenchyma.

The preliminary diagnosis of rheumatic fever was not corroborated post mortem. This point is stressed, as "rheumatism" is regarded by Fahr [13] as one of the etiologic factors in conditions characterized by "necrotizing arteriolitis"; neither the presence of pains in various parts of the body, including the periarticular portions of the joints, nor the pathologic evidence of vascular changes of the type just mentioned is pathognomonic of rheumatic fever as defined in its strict sense; the results of numerous postmortem examinations also speak clearly against that view which would make of dermatomyositis a rheumatic disease.

While hesitating, therefore, to disagree with so eminent an authority as Fahr, I think it probable that this is one of the few times when this investigator has employed the term "rheumatism" in an obscure sense.

Of equal importance was the implied diagnosis of hilus tuberculosis and the suggestion that the patient be segregated in a sanatorium. This opinion was based on a doubtful interpretation of a roentgenogram of the chest and the occurrence of an eruption diagnosed as lupus erythematosus, the supposition being that this rash indicated a tuberculous source. The consistently negative tuberculin tests, later in high dilutions, and the absence of active tuberculosis post mortem, despite a progressively severe course, are points that appear to eliminate satisfactorily this theory of cause. It has been pointed out that the evidence based on studies at necropsy is at variance with the hypothesis relating lupus erythematosus to tuberculosis directly and that the association is generally "coincidental and unrelated." There are, however, reasons for believing that in exceptional cases there may be an indirect relation, a stirring up of tuberculosis in lymph nodes which have been the former sites of this disease. In any event, it is clear that in case 4 there was no evidence of tuberculosis.

Likewise, no etiologic conclusions can be drawn from the observation of Streptococcus haemolyticus in a culture of blood taken just before the death of the patient, as it was probably the result of an invasion from a sacral decubitus ulcer. As previous bacteriologic investigations had been fruitless, it is likely that this represented an intercurrent complication prematurely closing the course.

REPORT OF CASE 5

The patient in this remarkable case was observed at the Sydenham Hospital in the service of Dr. I. Jesse Levy and was first seen by me through permission of Dr. A. Rostenberg Sr. From the beginning the condition was recognized as peculiar, and, despite opportunity for subsequent study, no unified opinion was reached. It is my belief, however, that the clinical features were those of dermatomyositis of an acute type, with associated findings that suggested periarteritis nodosa. The initial fulminating character of the condition and the surprising recovery that apparently ensued were remarkable, though the latter was followed by a transient relapse.

The patient, a 14 year old boy, born in the United States but of Spanish descent, was first observed on April 6, 1937. About one week before his admission there appeared a few reddish, painful swellings in the skin, gradually spreading to other portions of the body. He also complained of fever, chills and malaise. Shortly after, he noticed that the voided urine was red. He had an exquisitely sore throat, and swallowing was difficult. The eyelids and forehead became swollen, and he complained of severe pains in the limbs. There was no antecedent history of rheumatic fever or scarlatina.

On his admission a physical examination was carried out with difficulty, owing to the excruciating pain experienced by the patient on turning from side to side and on being touched. He appeared acutely ill. Examination of the heart revealed a tachycardia (140 beats in a minute); no murmurs were audible. The liver and spleen could not be palpated. The abdomen was neither rigid nor tender at this time. The face and all the limbs were sites of erythematous swellings which were warm to the touch and exquisitely tender, and which apparently involved the subcutaneous tissues as well. Among the diagnoses offered were multiple abscesses with bacteremia, acute rheumatic fever, periarteritis nodosa and acute bacterial endocarditis.

On April 7 a peculiar edema and redness of both the infraorbital and the supraorbital region were observed. The erythema extended down to the region of the nose, but the distribution did not precisely resemble that seen in the "butterfly" rash of lupus erythematosus. The movements of the eyeballs were normal; examination of the ocular fundi revealed no abnormalities. The throat was somewhat reddened, but no exudate was visible; a smear, however, showed pus cells and diplococci, and a culture revealed a pure growth of Str. haemolyticus. The temperature fluctuated between 101 F. and 103 F. On several occasions the urine was frankly hemorrhagic, and from the beginning examination of such specimens showed many red blood cells, white blood cells and occasional hyaline and granular casts. Analysis of the blood revealed: hemoglobin content, 63 per cent; red blood cell count, 4,280,000; white blood cell count, 54,600, with 93 per cent polymorphonuclear leukocytes. The content of urea nitrogen was 40.3 mg., indicating a moderate degree of azotemia. Other observers now felt that this was a case of acute lupus erythematosus.

On April 8 the outstanding feature was the presence of "nodular" thickenings distributed over various parts of the body, notably the limbs; these indurations were reddish blue and tender, and seemed to involve skin, subcutaneous tissue and muscle. The submental and left axillary glands were moderately enlarged. Because some of the cutaneous lesions had a purplish hue, it was believed that hemorrhage was present, and on this basis the suggestion of Henoch's purpura was advanced. A culture of blood, taken on admission, was now reported as sterile. Among the other diagnoses offered were acute periarteritis nodosa, dermatomyositis and erythema nodosum.

On April 9 several erythematous areas showing various attributes were observed. About the eyes, forehead and right forearm there were erythematous lesions that were not well demarcated. Over the upper aspect of the right thigh and on the right foot were two large, roughly oval patches with circumscribed, raised borders and relatively depressed centers; in the latter areas the skin felt taut and slightly indurated (edema?). Owing to the excruciating pain, a complete examination could not be carried out.

Several days later I saw the patient for the first time. The skin of the forearms, legs, thighs and feet revealed roughly oval and marginated patches, the dimensions of which ranged from 2 inches (5.08 cm.) to about 4 inches (10.16 cm.) in their longest diameters; the borders were erythematous, raised and irregularly contoured, whereas the centers were relatively depressed, though level with the surrounding skin, were brownish blue in some areas and paler in others and were edematous and somewhat tender when pinched or even when gently touched. How much of the tenderness was actually resident in the skin itself it was difficult to determine, for the effect of even slight manipulation was transmitted to the underlying structures, which were manifestly sensitive to pressure. A few erythematous, irregular

patches were observed on the integument overlying several knuckles and some of the phalangeal joints. The eyelids were puffy and discolored a reddish brown, the appearance and the clinical course differentiating these lesions from angioneurotic edema (fig. 4). The muscles of the limbs, especially the large bundles, were markedly swollen and painful to touch; pressure on the large muscular masses of the upper limbs revealed pitting edema, and it seemed probable that the subcutaneous fat was also implicated in the process. A few small, erythematous lesions capped by a whitish membrane were found on the buccal mucosa. Another culture of blood was sterile. In the interim, also, the anemia had become more extreme in the course of a few days. The hemoglobin content fell to 25 per cent; the red blood cell count was 1,320,000; the platelets numbered 370,000; the white blood cell count was 78,000 with 87 per cent polymorphonuclear leukocytes, of

Fig. 4 (case 5).—Discolored areas of edema involving the eyelids. The remainder of the eruption is acne vulgaris.

which about half were immature forms. The clinical picture was consistent with the diagnosis of dermatomyositis; however, the gross hematuria, the formed elements in urinary specimens, the modreate azotemia and the unusually high leukocyte count were features suggesting periarteritis nodosa. It may be parenthetically added that gross hematuria has been found in occasional instances of dermatomyositis (as in case 2 in this report).

A few days later the face was markedly swollen and indurated. Pressure applied to the cheeks caused pitting in the edematous infiltration, indicating that the swelling was largely due to the presence of edematous fluid. On the other hand, the limbs, which at first had shown pitting edema, now disclosed a firm, indurated condition. Several days later the skin of the face became firm and indurated as in "scleroderma," but the integument could still be lifted away from the main

subjacent mass. A roentgenogram of the chest revealed no abnormalities, aside from an increase in the size and density of the hilar shadows and the presence of some calcific deposits. It is interesting that the total protein content was 6.36 mg., with definite inversion of the albumin-globulin ratio (albumin 2.9 mg., globulin 3.46 mg.). Subsequently the patient complained of severe pain in the abdomen, and the tissues in this area were found to be diffusely swollen and excruciatingly painful to touch. Throughout this period the temperature was spiking and the pulse rate rapid, about 120 a minute. Some observers felt an enlarged liver, which seemed to indicate a degree of cardiac failure. In order to treat the edematous element in this case, the patient was put on a salt-free diet, and theobromine with sodium salicylate was administered per rectum.[35] Within several days a remarkable transformation occurred. Large amounts of fluid were voided; the edema of the subcutaneous tissues and muscles diminished, and the patient now appeared markedly emaciated, with muscular wasting apparent. The loss of subcutaneous fat and muscular tissue and the previous edematous stretching of the skin were further emphasized by the rapid appearance of striae atrophicae about the hips, knees, elbows and shoulders. Almost from the onset of the diuretic effect, the patient felt better; he no longer complained of pain in the parts that formerly could not be touched without a reaction of agonizing pains.

On May 16 a sacral decubitus ulcer appeared and was regarded apprehensively. Despite the poor condition of the patient, the defect in the skin closed slowly and spontaneously. The content of urea nitrogen, which on admission had been 40.3 mg., steadily diminished until it reached the level of 18.1 mg. A single determination of the content of calcium in the blood showed it to be 8.8 mg.; the phosphorus in the blood was 3.9 mg. The blood pressure was not elevated at any time, an average reading being 126 systolic and 70 diastolic. Examination of urinary specimens continued to show red blood cells, white blood cells and a few hyaline and granular casts. The temperature slowly fell to normal, with occasional interspersed rises. On one occasion a culture of blood revealed an organism in the fluid medium, at first regarded as Str. viridans, but later identified as Str. haemolyticus. The significance of this finding was somewhat indefinite, but it was decided to administer sulfanilamide. After the intake of the drug, the temperature assumed a normal level and the succeeding cultures of blood were sterile. Nevertheless, the efficacy of sulfanilamide in this case could be questioned, for the bacteriologic findings were of dubious significance, especially in view of the several previous sterile results; the subsequent course was occasionally subfebrile; the tachycardia remained constant, and the patient returned with an exacerbation of the condition. It seems more likely that the results achieved were coincidental, for, aside from an occasional rise in temperature, the patient appeared to be on the road to recovery. After several months of observation, he was sent home, and although there was no fever, the pulse rate hovered about 120 in a minute. Shortly before his discharge from the hospital, the white cell count was 11,000 with 53 per cent polymorphonuclear leukocytes, 43 per cent lymphocytes, 2 per cent eosinophils and 2 per cent monocytes.

Early in the course a piece of skin and muscle was excised for diagnostic purposes. Regarding the pathologic changes and their interpretation, there was some difference in opinion. In addition, the specimen did not contain enough muscular tissue to insure an adequate examination and, moreover, was removed from an area of the body (leg) where the indurative process in the muscles was less conspicuous clinically. The specimen was immediately fixed. It is my

35. Levy, I. J.: Personal communication to the author.

purpose to report the observations as interpreted by me and to indicate in what respects others disagreed, so that an unprejudiced account may be given.

The material consisted of two separate specimens. One was an elliptic piece of skin and subcutaneous fat, 3.5 by 1.25 by 1 cm. There was no evidence of erythema. On section the tissue was semifirm, and the epithelial layers were not thickened. Another piece of tissue seemed to be muscle; it was a light, grayish-red and presented no other gross pathologic alterations (Dr. A. E. Eisenberg). On microscopic study the following changes appeared significant: The muscle tissue was edematous. Many of the fibers revealed hyaline degeneration, with loss of the transverse striations. In several areas there were accumulations of nuclei that appeared to represent proliferations of sarcolemma nuclei. The blood vessels situated interstitially were sites of a conspicuous infiltration composed chiefly of cells located in the adventitial layer, and apparently these represented an increase in the adventitial cells. Although the blood count had shown an unusual polynucleosis, polymorphonuclear leukocytes were scant. In the interstitial spaces, also, there was evidence of an edematous process.

In the subcutaneous fat there were similar changes in many blood vessels. There was, moreover, in some areas what appeared to be a proliferation of young fat cells, with occasional granulomatous formations. These alterations recalled to my mind the findings in the adipose tissue as recorded by Weber and Gray [36] in their report of a case of poikilodermatomyositis.

In the skin proper the changes were chiefly in the deeper layers adjoining the hypoderm. There the bundles of collagen were edematous and stained a pale pink. The vessels showed thickening of the parietes owing to infiltration of fluid and hyaline degeneration; there were occasional collections of nuclei in the subendothelial layer, with narrowing and tendency to closure of the lumens. The vessels were surrounded by periadventitial accumulations of fixed connective tissue cells, a few polymorphonuclear leukocytes and an occasional lymphocyte. Similar, though much milder, changes were observed in the more superficially situated blood vessels in the skin.

There was agreement that the principal pathologic effects had been exerted on the blood vessels in the deeper parts of the skin, subcutaneous tissue and muscle. The chief point of disagreement concerned the interpretation of the observation in the muscle proper. It was, however, conceded that this tissue was edematous and somewhat degenerated (as described in the gross description) and that the wasting observed in this boy was at least partially caused by the loss of muscular parenchyma. It was also agreed generally that the findings were insufficient for the diagnosis of periarteritis nodosa.

Addendum.—Several months later the patient was again admitted to the hospital during an acute exacerbation of the disease. The outstanding feature at this time was the occurrence of several subcutaneous lumps in the lower limbs giving rise to the clinical impression that the condition was one of periarteritis nodosa. Microscopic examination of one of these lesions showed only normal fat and it is possible that the nodule was missed. It is also interesting that on this occasion the musculatures of the upper and lower limbs seemed to approximate a normal state, though their mass was still considerably diminished. It is planned to observe the patient further.

36. Weber, F. P., and Gray, A. M. H.: Chronic Relapsing Polydermatomyositis with Predominant Involvement of the Subcutaneous Fat (Panniculitis), Brit. J. Dermat. **36**:544, 1924.

COMMENT ON CASE 5

The painful masses of muscle with redness of the overlying integument, the erythematous and edematous swellings about the eyes, the lesions over some of the knuckles and interphalangeal joints and the febrile state, appeared to be consistent with the diagnosis of dermatomyositis. The unusual features were the gross hematuria (sometimes observed in cases of dermatomyositis), the urinary findings, the moderate azotemia and the abnormally high leukocyte count, these anomalies apparently pointing toward periarteritis nodosa. It seemed evident that the chief effects were resident in the blood vessels, though the alterations were not nearly so pronounced as in the "necrotizing arteriolitis" described by Fahr in his report of a case of dermatomyositis. It appears that the primary changes occurred in the vasculature, with secondary effects on the tissues supplied by the affected vessels.

It is interesting that early in the course the muscular swellings in the limbs pitted on pressure and that within a short time the affected areas became indurated and then failed to show pitting. On the face the condition on the latter occasion appeared to be scleroderma, but the skin could still be lifted away in fairly supple folds from the underlying tissue. It is therefore probable that the attribute of firmness was dependent on the degree and type of edematous infiltration occurring in the deeper tissues.

Remarkable was the transformation observed in this patient after the loss of fluid from the tissues, which was brought about by the method stressed by Dr. I. Jesse Levy.[35] Forthwith, the element of pain was relieved, and tissues that at first responded with excruciating pain to touch, now could be handled without pain. The evidence appeared to support the belief of those who thought there was a degree of cardiac failure. In recent years there has arisen a body of opinion that stresses the element of myocardial alterations in occasional instances of dermatomyositis; this aspect of the subject needs further investigation.

The simultaneous involvement of subcutaneous tissue and skin as well as of muscle is a point to stress. The occurrence of striae atrophicae can be attributed to the distention of the superficial tissues by edematous fluid, followed by loss of water; in principle, this is similar to what happens in pregnant women and in persons who have lost weight after a previous state of obesity.

Finally, the persistent tachycardia manifested by this patient is a phenomenon that is often observed in dermatomyositis; its precise genesis is still unknown, though it seems probable that it is bound up in some way with damage to the heart. Such tachycardia may occur in patients with a subfebrile or even normal temperature.

SUMMARY

The protocols of 5 cases are recorded in detail in order to depict the varied manifestations of dermatomyositis as well as to illustrate what may be called a condition "transitional" between that disease and systemic lupus erythematosus. Additional examples of this condition are mentioned only in connection with the elaboration or substantiation of certain points. A preliminary attempt is made to clear the ground for a more detailed consideration of the similarities and the differences in the clinicopathologic features exhibited by each of these diseases in their typical forms.

Two instances of dermatomyositis are described, one very briefly, in which there appeared suggestive evidence that the factor of lead played an important part in the evolution of the clinical picture. These cases are not isolated and are considered in relation to the data indicating that this heavy metal is a vascular poison, especially in certain susceptible persons. These data are carefully reviewed, notably because there is a tendency on the part of observers to attribute various diseases to lead absorption; whenever such views are advanced, critical investigators have, with considerable justification, refused credence to them. Moreover, the cases under my observation did not present the classic evidence of plumbism. Nevertheless, it is suggested that lead may exert a deleterious effect on the blood vessels in especially susceptible persons with a presumably unstable vascular system, and in such persons "vascular disease may be and remain the solitary sign of lead poisoning." The connection between this heavy metal and vascular disease is regarded as probable, even though specific or pathognomonic lesions are not produced. The evidence compiled in this paper cannot be summarily dismissed without further investigation of the problem, which is admittedly difficult.

EFFECTS OF ROENTGEN THERAPY ON HISTOLOGIC PICTURE AND ON SURVIVAL IN CASES OF PRIMARY CARCINOMA OF LUNG

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It is the purpose of this paper to present (*a*) a study of the histologic effects of roentgen therapy on primary cancer of the lung, made in an effort to determine the degree of radiosensitivity of this tumor with special reference to its different histologic types, and (*b*) a study of the effects of roentgen therapy on the period of survival in cases of carcinoma of the lung.

The idea is prevalent in some places that irradiation is the therapy of choice for primary carcinoma of the lung. Is this view justified? In their accompanying and complementary paper Bloch and Bogardus [1] have presented evidence, based on clinical improvement and on longevity following irradiation, that such treatment is not curative. A search of the literature by them disclosed no authentic cure by irradiation. In postmortem studies I have not observed a primary cancer of the lung to which a lethal dose of roentgen therapy had been given. In fact, the usual experience has been to find that the effect of irradiation, as judged by histologic standards, was far from carcinocidal. It is in an attempt to evaluate the degree of this deficiency that the present study is presented, and it is hoped that by estimation of the effectiveness of technics in use at present the steps necessary to improve therapy will be clarified.

The material on which this study is based consists of 21 patients with primary cancer of the lung who received roentgen therapy and 64 nonirradiated patients used as controls, all of whom have been studied post mortem by members of the department of pathology of the University of Chicago. A study of five irradiated metastatic lesions from carcinoma of the lung is also included. There is a considerable overlap in this series and that studied by Bloch and Bogardus, but the material is not identical, each including many patients not present in the other series. Minor differences consequently appear in the analyses in the two papers, but the general conclusions coincide.

From the Department of Pathology of the University of Chicago.

1. Bloch, R. G., and Bogardus, G.: Bronchogenic Carcinoma, with Special Reference to Results with Roentgen Therapy, Arch. Int. Med., this issue, p. 39.

All of the patients, with 2 exceptions, were treated with 200 kilovolts. Most of them were treated with 25 milliamperes, with a few exceptions, in which 5 and 10 milliamperes were used. The half value layer was usually 1.6 mm. of copper. The usual focal skin distance was 50 cm., although 5 patients were treated at 80 cm. The primary tumors were usually treated by using three 15 by 15 cm. thoracic portals, located anteriorly, laterally and posteriorly. Except in a few instances one portal was treated daily. Further details of treatment are given in the tables and also in each individual case report.

HISTOLOGIC EFFECTS OF IRRADIATION ON CARCINOMA OF THE LUNG

For purposes of analysis the 21 cases have been divided into four groups, according to the tumor dose.

Group 1 (5,000 to 3,020 r).—Five patients received irradiation varying from 5,000 to 3,020 r as calculated for the primary tumor. The

TABLE 1.—*Carcinomas Treated with 5,000 to 3,020 Roentgens*

Case	Time of Roentgen Treatments in Days Before Death		Tumor Dose, Roentgens	Histologic Type of Tumor	Histologic Effects
	First	Last			
1	182	121	5,000	Undifferentiated carcinoma	Slight increase in fibrous tissue
2	103	66	4,250	Undifferentiated carcinoma	Necrosis, fibrosis and anaplasia
3	51	27	3,820	Adenocarcinoma	Necrosis, fibrosis and anaplasia
4	169	64	3,450	Undifferentiated carcinoma	Marked necrosis, slight fibrosis and anaplasia
5	152	126	3,020	Squamous cell carcinoma	None

time of the treatment with respect to when the histologic analysis was made, the dosage, the histologic type of tumor and the general results are given in table 1. Other details of the treatment are given in the individual case report. Although 3 of the 5 tumors showed rather marked damage, in no instance was a carcinocidal effect achieved. Two of these 3 tumors showed severe damage, which was lethal to many cells. They were respectively an adenocarcinoma and a completely undifferentiated carcinoma. The third tumor, which showed considerable but less damage, was also an undifferentiated carcinoma. Of this first group of 5 tumors which received large doses, 2 showed no histologic changes attributable to the roentgen treatment. One of these was a highly undifferentiated carcinoma which received 5,000 r. The other was a squamous cell carcinoma which showed considerable keratinization, part of which may, however, have been stimulated by the irradiation.

REPORT OF CASES

CASE 1.—This case was one of anaplastic, highly undifferentiated carcinoma (fig. 1). Except for a slight increase in fibrous connective tissue no histologic changes could be seen which might be attributed to the irradiation, although it is noteworthy that one hundred and twenty-one days had lapsed since the last treatment was given, and some recurrence of the tumor cells might have taken place to obscure changes previously present. The tumor was composed of small, oval, closely packed cells with very little cytoplasm and dark, dense nuclei. In general

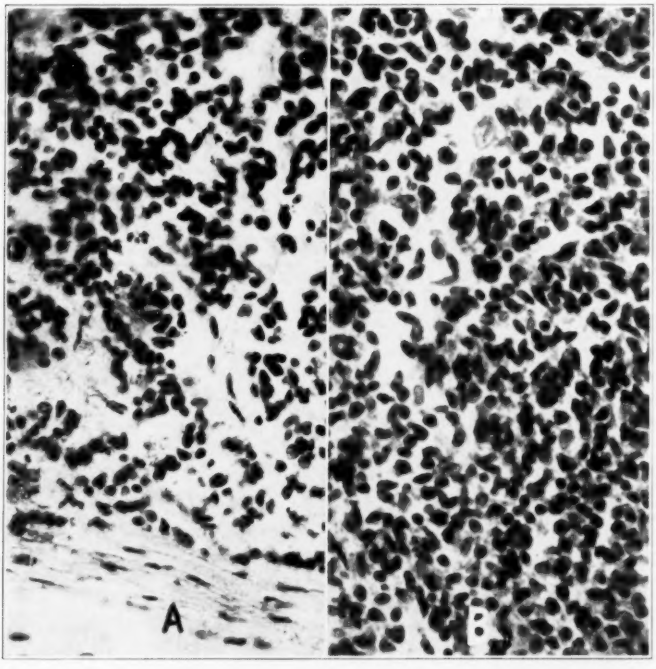

Fig. 1 (case 1).—Photomicrographs (× 375) showing the appearance of the irradiated primary lesion in the lung (*A*) and of a typical nonirradiated metastatic lesion (*B*). Note the relatively small amount of change produced by 5,000 r.

these cells grew diffusely, but in some metastases, notably the hepatic, they were piled up in thick layers which vaguely resembled transitional epithelium, although the cells themselves did not look like transitional cells. No necrosis was seen at any place in the tumor, and no change had been induced in cell type. Fifteen treatments of 550 r each, the effective dose as measured on the skin, were given in twenty-one days. After a four week rest period fourteen treatments of 550 r each were given in sixteen days.

CASE 2.—The cells resembled those in case 1, except that they were slightly larger and showed more variation in size (fig. 2). The primary tumor, however, showed moderate changes attributable to roentgen therapy when compared with its metastases. There was marked fibrosis in the primary tumor, but since there was evidence of healed tuberculosis in this region also, the degree of fibrous increase produced from the tumor alone is uncertain. In this fibrous tissue the tumor cells showed marked anaplasia and great variation in size, shape and staining reactions when compared with the distant metastases. While some cells had small pyknotic nuclei, others showed large pale or hyperchromatic nuclei, some

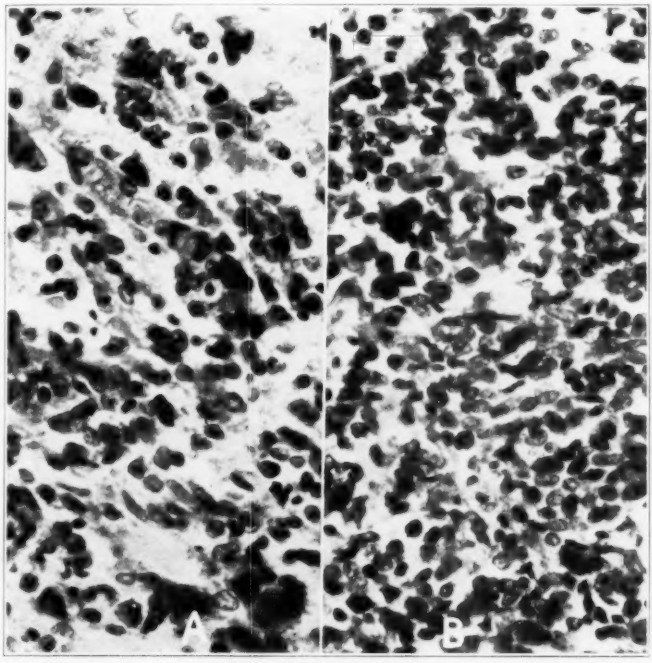

Fig. 2 (case 2).—Photomicrographs (× 375) showing the moderate changes induced in a cellularly undifferentiated type of carcinoma of the lung (*A*) by 4,250 r, with a typical nonirradiated metastatic lesion (*B*) for comparison.

of which were lobulated or even multiple. The cellular cytoplasm was more abundant, and it tended to be more acidophilic. In many places cells had fused to form syncytial masses or giant cells, and in other regions nuclei had degenerated, releasing masses of chromatin dust. Thirty-two treatments of 340 r each, the effective dose as measured on the skin, were given in thirty-seven days.

CASE 3.—The tumor was a well differentiated adenocarcinoma with tall columnar mucus-secreting cells which after irradiation showed marked degeneration and disorganization of structure. The arrangement of cells into glands was lost, and the cells were separated and showed marked dedifferentiation or anaplasia,

with numerous giant cells. There were much cell necrosis and lesser degrees of cell damage, consisting of edema and vacuolation of cytoplasm with an increased affinity for acid dyes, with marked pyknosis or karyorrhexis in the nuclei. This case has been previously described in detail by Steiner and Francis,[2] and additional photomicrographs are shown in figure 3. The patient was given five treatments of 230 r in five days, followed by thirty-four treatments of 310 r, the effective dose as measured in air, in twenty-five days.

CASE 4.—The tumor was an undifferentiated carcinoma similar to those in cases 1 and 2. The primary lesion in the lung showed marked retrogressive changes

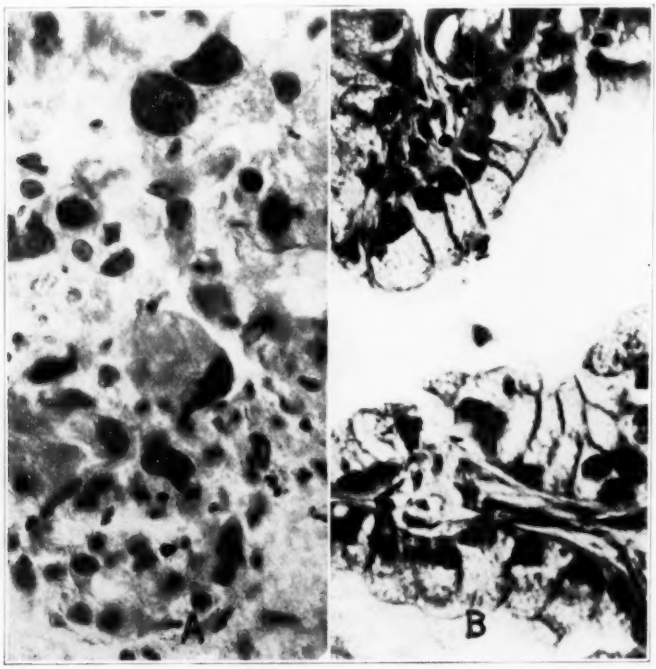

Fig. 3 (case 3).—Photomicrographs (× 375) showing the marked changes produced in a primary adenocarcinoma of the lung (*A*) by 3,820 r and the appearance of a nonirradiated metastatic lesion (*B*).

attributable to roentgen radiation when compared with the metastases in the nonirradiated liver. There was much active cell degeneration and necrosis, with pyknosis, karyorrhexis and karyolysis, but marked alterations in general cell type were not seen. The patient received 3,600 r in thirty-eight days at another institution, followed by six treatments of 250 r, measured on the skin, in seven days.

2. Steiner, P. E., and Francis, B. F.: Primary Apical Lung Carcinoma, Am. J. Cancer **22**:776-785 (Dec.) 1934.

CASE 5.—The tumor was a squamous cell carcinoma which showed no recognizable changes attributable to roentgen radiation. Keratinization may have been induced or hastened, but unfortunately there were no nonirradiated distant metastases available for comparison. Twenty treatments of 325 r, the effective dose as measured on the skin, were given in twenty-six days.

Group 2 (1,890 to 1,035 r).—A tumor dose of 1,890 r to 1,035 r was given in 9 cases, which are summarized in table 2. In this group are 4 examples of squamous cell carcinoma, of which 3 showed marked but sublethal roentgen effects. Two poorly differentiated adenocarcinomas showed no recognizable damage from the irradiation. Two undifferentiated, small-celled carcinomas likewise showed no marked changes. The remaining tumor, a papillary adenoma malignum, also known as bronchial carcinoid or basal cell carcinoma of the bronchus, showed do damage.

TABLE 2.—*Carcinomas Treated with 1,890 to 1,035 Roentgens*

Case	Time of Roentgen Treatments in Days Before Death: First	Time of Roentgen Treatments in Days Before Death: Last	Tumor Dose, Roentgens	Histologic Type of Tumor	Histologic Effects
6	1,091	742	1,890	Malignant adenoma	None
7	34	20	1,850	Undifferentiated carcinoma	None
8	232	220	1,740	Squamous cell carcinoma	None
9	9	1	1,670	Squamous cell carcinoma	Acute degeneration, edema and anaplasia
10	14	2	1,490	Squamous cell carcinoma	Necrosis and anaplasia
11	59	22	1,282	Adenocarcinoma	None
12	104	70	1,150	Undifferentiated carcinoma	None, except possibly fibrosis
13	39	29	1,056	Squamous cell carcinoma	Necrosis, fibrosis and anaplasia (roentgen effect?)
14	123	89	1,035	Adenocarcinoma	None

CASE 6.—The tumor was an undifferentiated small round to oval cell carcinoma of the papillary adenoma malignum type. Its growth was chiefly intrabronchial but with slight infiltration into the adjacent parenchyma of the lung and metastases only to adjacent peribronchial lymph nodes, in spite of the long duration of the disease. There were no retrogressive changes which could be attributed to irradiation and fewer degenerative changes than would be expected from the age of the tumor. Eleven treatments of 270 r each and eight of 310 r each were given during eight months.

CASE 7.—The tumor was a highly undifferentiated and anaplastic carcinoma composed of medium-sized, often polyhedral cells, with a few tumor giant cells, lying in a dense fibrous stroma. There were no visible degenerative changes corresponding to the fairly recent irradiation, and the fibrosis and cellular anaplasia which were present in the pulmonary tumor were equally great in nonirradiated metastases. Ten treatments of 400 r, the effective dose as measured on the skin, were given in fifteen days.

CASE 8.—The tumor was a recurrent lesion in the bronchial stump of a squamous cell carcinoma showing keratinization of single cells or of small groups of cells. Although it had been irradiated with 1,740 roentgen units, it did not appear different from a bronchoscopic biopsy section secured prior to irradiation or from sections

made from the tumor which was removed by pneumectomy, also before irradiation. This amount of radiation had not noticeably hastened keratinization or induced anaplasia. It was too long after irradiation to determine whether cell necrosis had been produced, and the differences in the amounts of fibrous tissue are not significant. Twelve treatments of 328 r, the effective dose as measured on the skin, were given in twelve days.

Case 9.—The tumor showed the acute effects of irradiation, therapy having been begun nine days before death and continued until the day before death (fig. 4). Elsewhere the tumor was a squamous cell carcinoma with healthy-appearing cells

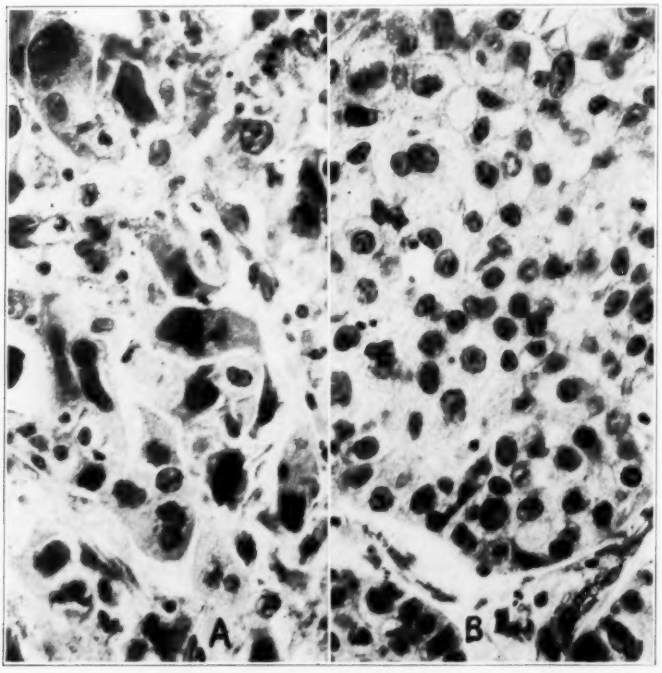

Fig. 4 (case 9).—Photomicrographs (× 375) showing the marked changes produced in a primary squamous cell carcinoma of the lung (*A*) by 1,670 r and the appearance of a nonirradiated metastatic lesion (*B*).

growing in broad sheets. Keratinization was confined to single cells, and an occasional tumor giant cell was seen. In the irradiated primary tumor, however, edema, anaplasia and acute degenerative changes were seen. The cell masses were distorted or broken up. The cells were separated by intercellular edema and had become rounded. Many giant cells were present. Many cells showed marked vacuolation of their cytoplasm, which in general appeared increased in amount and stained more deeply with eosin. Nuclear changes were also marked and consisted of giant and multiple nuclei, karyorrhexis, some karyolysis and considerable pyknosis. Thirteen treatments of 330 r, the effective dose as measured on the skin, were given in eight days.

CASE 10.—This tumor also showed the effects of recent irradiation. Therapy was given from fourteen days to two days before death and was calculated as 1,490 r. The changes consisted of massive necrosis, marked anaplasia and some evidence of hastening of maturation, the irradiated primary tumor being more easily recognizable as a squamous cell carcinoma than were the distant metastases, in which the tumor tissue was more undifferentiated and small celled. The necrosis was massive and was not confined to the poorly nourished centers of cell masses. The cells were separated from each other, were rounded and showed marked variation in size, shape and chromatin content. Bizarre cell forms and giant cells were numerous. In general, the changes resembled those illustrated in case 9, except that necrosis was much greater, edema was less and there was some evidence of hastening of the cell maturation cycle. Nine treatments of 400 r, the effective dose as measured on the skin, were given in twelve days.

CASE 11.—The tumor was an undifferentiated adenocarcinoma which showed no changes which could be attributed to irradiation with certainty, although the treatment had been given fairly recently. Retrogressive changes consisting of necrosis and fibrosis were present to approximately equal degrees in the primary tumor and in its metastases. Twelve treatments of 280 r, the effective dose as measured on the skin, were given in fifteen days. After a rest period of three weeks, two treatments (at the same dosage) were given on consecutive days.

TABLE 3.—*Carcinomas Treated with 975 to 480 Roentgens*

Case	Time of Roentgen Treatments in Days Before Death: First	Time of Roentgen Treatments in Days Before Death: Last	Tumor Dose, Roentgens	Histologic Type of Tumor	Histologic Effects
15	263	118	975	Adenocarcinoma	None
16	145	119	910	Adenocarcinoma	None
17	135	133	670	Adenocarcinoma	None
18	14	13	480	Undifferentiated carcinoma	None

CASE 12.—The tumor was an undifferentiated, small, oval to round cell carcinoma in which the primary tumor differed from its metastases only in containing more fibrous tissue. There was no alteration in the morphologic character of the tumor cells. Twelve treatments of 275 r, the effective dose as measured in air, were given in thirty-four days.

CASE 13.—The tumor was squamous cell carcinoma which showed massive necrosis, marked fibrosis and some cell anaplasia. The role which irradiation played in producing these changes is uncertain, because there were few nonirradiated metastases for comparison. Adjacent to areas showing marked degenerative changes were sheets of fairly healthy-appearing cells. These may, however, have appeared after irradiation. In general the changes resembled those seen in case 10. Eight treatments of 275 r, the effective dose, were given in ten days.

CASE 14.—The tumor was an undifferentiated adenocarcinoma in which no changes due to irradiation were visible. Twelve treatments of 350 r, the effective dose as measured on the skin, were given in thirty-five days.

Group 3 (975 to 480 r).—In group 3 are placed 4 cases in which the cancers received between 975 r and 480 r (table 3). There was no evidence of irradiation effect in any tumor in this group.

CASE 15.—The tumor was a moderately well differentiated adenocarcinoma which showed no change recognized as due to roentgen therapy. It was moderately

scirrhous in its metastases as well as in the primary lesion, and degenerative changes were approximately equal in all regions. Fourteen treatments of 118 r were given in sixty-seven days.

Case 16.—The tumor, an adenocarcinoma with colloid features, appeared well preserved and approximately identical in all lesions, both primary and metastatic. Nine treatments of 350 r, the effective skin dose, were given in twenty-six days.

Case 17.—The tumor was a well differentiated adenocarcinoma producing much mucin. There was no visible effect of roentgen therapy. Three treatments of 460 r were given on three consecutive days.

Case 18.—The tumor was an undifferentiated carcinoma composed of medium small, dense, compact oval to round cells. It showed no effect of roentgen therapy. Two treatments of 480 r were given in two days.

Group 4 (Unkown Amount).—The pulmonary cancers of 3 other patients were treated by roentgen therapy. The amounts given are not known. In 2 instances the microscopic examination revealed no damage which might be attributed to the roentgen ray. In the remaining case there were degenerative changes, but they were not great, were not definitely due to roentgen damage and were certainly not nearly lethal for the tumor cells.

Case 19.—The primary lesion of the tumor, a large-celled, undifferentiated carcinoma, showed a greater degree of fibrosis and also more recent necrosis than did most of its metastases, except those in the mediastinal lymph nodes. Regardless of whether these changes were induced by roentgen therapy, most of the tumor cells appeared undamaged, and a carcinocidal effect had not been approached. The last treatment had been given twenty-one days before death.

Case 20.—The tumor, an undifferentiated adenocarcinoma, showed no changes suggestive of roentgen damage.

Case 21.—The tumor was an undifferentiated squamous cell carcinoma which showed no damage from the roentgen rays.

HISTOLOGIC EFFECTS OF IRRADIATION ON METASTASES OF CARCINOMA OF THE LUNG

A study has also been made of the histologic effects of roentgen radiation on metastases of carcinoma of the lung in an effort to get further information on its radiosensitivity. Five cases are summarized in table 4. Case 22 is that of a metastasis to the skull in which microscopic examination sixty days after irradiation failed to disclose any living tumor cells. This, therefore, respresents the only instance in this entire survey in which a complete carcinocidal effect was observed. It is possible that a more complete microscopic examination might have disclosed some living cells in this instance.

Case 22.—This was the only example encountered in which the cells of a pulmonary carcinoma were killed. The tumor was a cranial metastasis from a primary carcinoma of the lung which was composed of large pleomorphic cells, diffusely growing and undifferentiated. Sixty days after 3,800 r had been delivered to this metastatic lesion it showed no definitely recognizable tumor cells, although a few pyknotic nuclei entrapped in dense collagen may have been forms of surviving

tumor cells. Five treatments of 370 r were given in five days. After a rest period of one week a second course of the same dose was given. After three days of rest five treatments of 245 r were given in five days.

CASE 23.—The effects of 3,820 r on the primary adenocarcinoma of the lung in this case have been described under case 3. Metastases into the lower cervical vertebral bodies were treated with 2,520 r seventeen days prior to death. Microscopic examination of these bony metastases showed them to resemble a metastasis in the ilium which had not been irradiated. Whether this failure to produce damage to the carcinoma cells was due to protection by bone or whether it indicates true radioresistance is impossible to say. Eight treatments of 415 r were given in nine days.

CASE 24.—A metastasis in the right ilium, treated with 1,640 r, resembled the primary tumor and numerous other metastases, including some in nonirradiated bones. The tumor was an adenocarcinoma. Eight treatments of 325 r were given in twelve days.

CASE 25.—An irradiated metastasis in the brain in this case of carcinoma with pleomorphic, large undifferentiated cells showed a marked degenerative change

TABLE 4.—*Effect of Irradiation on Metastases*

Case	Treatment in Days Prior to Autopsy		Tumor Dose, Roentgens	Site of Metastasis	Histologic Type	Effects of Irradiation
	First	Last				
22	80	60	3,800	Skull	Undifferentiated carcinoma	Lethal to tumor
23	26	17	2,520	Vertebral bodies	Adenocarcinoma	None
24	36	24	1,644	Pelvis	Adenocarcinoma	None
25	245	229	1,290	Brain	Undifferentiated carcinoma	None
26	264	239	860	Vertebral body	Adenocarcinoma	None

consisting of massive necrosis and heavy infiltration by polymorphonuclear leukocytes. In general, only cells adjacent to blood vessels remained alive. This necrosis, however, cannot be entirely, if at all, attributed to the therapy, because much of it was recent, whereas the last irradiation had been given two hundred and twenty-nine days prior to death. Twelve treatments of 225 r were given in twenty days.

CASE 26.—An irradiated metastasis in the tenth dorsal vertebral body showed no effects of the irradiation. This lesion was fibrous, but no more so than were nonirradiated metastases. Five treatments of 260 r were given in six days.

SUMMARY OF HISTOLOGIC CHANGES PRODUCED IN CARCINOMA OF THE LUNG BY ROENTGEN THERAPY

In general, the changes produced by roentgen rays were degenerative in the acute stages and retrogressive in the later stages, accompanied in some cases by profound alterations in cell type. None of the individual changes alone are specific for roentgen effects, but taken together at the various intervals the changes are fairly diagnostic. Among the 64 nonirradiated controls many instances of degenerative and retrogressive changes were seen which resembled those observed in the irradiated patients, yet the total picture produced by these changes in

any one case was unlike those produced by roentgen rays in individual cases. In evaluating the changes seen in irradiated tumors some reliance was placed on the comparative appearance of their metastases and, in a few instances, on biopsy sections secured prior to therapy.

The most acute changes were seen in cases 9 and 10. They consisted of intracellular and intercellular edema, vacuolation of cytoplasm with an increased affinity for acid dyes and some actual cell necrosis. The nuclear changes at this stage were degenerative and consisted of karyorrhexis, karyolysis or pyknosis. The later stages were those of disorganization of the architecture of the tumor growth and alteration of cell type. As a result of the former, adenocarcinomas lost their ductal or tubular appearance and became more undifferentiated (case 3), and in squamous cell carcinomas the arrangement of cells into squamous epithelium-like layers was lost. Changes in cellular morphologic structure concerned both the cytoplasm and the nucleus. The cells became enlarged, some reaching giant sizes. The cytoplasm stained more deeply with eosin, and it was often granular or vacuolated. The nuclei became more chromatic and were sometimes pyknotic. They tended to be enlarged, and multiple nuclei, ring nuclei, eccentrically placed nuclei and similar phenomena were common. These cellular changes were those of anaplasia or increase in undifferentiation, rather than metaplasia. At this stage there was an increase in fibrous connective tissue in the tumor. This was certainly a relative, and probably an actual, increase.

The number of cases is too small and the factors in therapy are too varied to warrant final conclusions as to the lethal dose and the relative radiosensitivity of the different histologic types of cancer of the lung. However, the evidence presented indicates that the lethal tumor dose would probably be over 5,000 r, although striking effects are produced by smaller doses. The small undifferentiated carcinomas with dark, hyperchromatic nuclei and scanty cytoplasm were less radiosensitive than were the adenocarcinomas and squamous cell carcinomas (tables 1 and 2). This finding was unexpected, because such cells appear more embryonal and undifferentiated, and from knowledge of radiosensitivity of tumor cells in general they would be expected to be more radiosensitive, than are the more highly differentiated types. Nevertheless, the observed fact is that these undifferentiated carcinomas are highly radioresistant.

Perhaps squamous cell carcinoma of the lung can eventually be added to the list of squamous cell carcinomas which are curable by irradiation. This group at present consists principally of carcinoma of the skin, lip, tongue, larynx and cervix of the uterus.

The postmortem histologic examination was made at approximately the time of maximum cellular damage in a few cases, but a glance

at the tables reveals that in others the interval between treatment and examination was so great that much recovery and proliferation of tumor cells had probably occurred. This has been taken into consideration in the text under the individual cases. In the instances in which the interval was great this study does not serve to contribute to knowledge of the radiosensitivity of these tumor cells, but it does give evidence as to their "radiocurability." Effects of radiation on carcinoma of the cervix were studied by serial biopsies by Arneson and Stewart,[3] who observed fully active regeneration of carcinoma one to six weeks after the termination of roentgen treatment. It is probable, therefore, that the healthy appearance of the tumor cells in some of the cases presented here is explained by regeneration after the therapy ceased. While this consideration may alter conclusions as to radiosensitivity, it does not affect those made with respect to radiocurability.

Data on the radiosensitivity of carcinoma of the lung comparable to these are scanty in the literature. One of the best studies is that by Herrnheiser,[4] who stated that the lethal dose is about 9,000 r, measured on the skin. The patient of Jacox [5] received 8,400 r (measured in air) in twenty-five days for an apical pulmonary tumor of undetermined histologic type, with temporary improvement. Frissell and Knox [6] stated that in their case XXXVII 5,400 r (measured where ?) given during five months caused little improvement of a cuboidal cell tumor. For other references the reader is referred to the monograph by Simons.[7]

EFFECTS OF ROENTGEN THERAPY ON ADJACENT TISSUES AND ORGANS

Observations were made on the condition of tissues and organs which lay near irradiated primary carcinomas of the lung in an effort to detect any possible harmful effect. The adjacent lung tissue, the pleural cavities, the pericardial cavity, the heart, the esophagus and the overlying skin were studied for this purpose. Changes were observed only in the skin, and they were of the types which usually follow such therapy.

3. Arneson, A. N., and Stewart, F. W.: Clinical and Histologic Changes Produced in Carcinoma of the Cervix by Different Amounts of Roentgen Radiation: A Comparison, Arch. Surg. **31**:542-567 (Oct.) 1935.

4. Herrnheiser, G.: Weitere Erfahrungen mit der Röntgenbehandlung maligner Bronchus- und Lungengeschwülste, Strahlentherapie **52**:425-459 (March) 1935.

5. Jacox, H. W.: Superior Pulmonary Sulcus Tumor, J. A. M. A. **103**: 84-87 (July 14) 1934.

6. Frissell, L. F., and Knox, L. C.: Primary Carcinoma of the Lung, Am. J. Cancer **30**:219-288 (June) 1937.

7. Simons, E. J.: Primary Carcinoma of the Lung, Chicago, The Year Book Publishers, Inc., 1937.

Adjacent Lung.—Although a systematic study of lung tissue through which roentgen rays passed to reach a carcinoma of the lung was not carried out, in the gross descriptions and microscopic sections which are available no important changes definitely due to the therapy were noted. Postmortem material such as this, however, in general is not suitable for accurate studies on this point, because the terminal infections and circulatory disturbances which are so commonly present in carcinomatous lungs complicate and obscure changes which the roentgen treatment may have produced. Pulmonary damage of the types described by Downs,[8] Schairer and Krombach[9] and others was not encountered in this study.

Pleural Cavity.—The incidence of pleural effusions, focal fibrous pleural adhesions or obliterative fibrous pleuritis on the side of the pulmonary cancer was no greater in the 21 patients who had received roentgen therapy than in the 64 nonirradiated controls. The incidence of such changes was greater on the side of the tumor than on the opposite side in each group.

Pericardial Cavity.—The incidence of pericardial effusions and of pericardial adhesions likewise was not greater in the irradiated patients than in those whose tumors had not been irradiated.

Heart.—Although fibrous myocardial scars were encountered often in the patients who had received roentgen therapy for pulmonary tumors, the incidence of such focal fibrous myocarditis was no greater than in the nonirradiated patients or in the general postmortem experience with persons of this age group.

Esophagus.—No changes were encountered in the esophagus which might have been caused by the roentgen treatment. The incidence of esophageal erosions, peptic esophagitis and leukoplakia of the esophagus was about equal in the irradiated and in the control patients.

EFFECTS OF ROENTGEN THERAPY ON SURVIVAL

The average period of survival after the onset of symptoms in the 53 nonirradiated control patients in whose cases data were available was ten and five-tenths months. The 21 patients treated with roentgen rays survived for an average of eleven and nine-tenths months after the onset of symptoms. This seems to indicate that the irradiation was slightly effective in prolonging life. However, when the following facts are taken into consideration it is clear that the irradiation had no such beneficial action. 1. The series in which irradiation was used included

8. Downs, E. E.: Lung Changes Subsequent to Irradiation in Cancer of the Breast, Am. J. Roentgenol. **36**:61-64 (July) 1936.

9. Schairer, E., and Krombach, E.: Röntgenstrahlenschädigung der Lunge mit tödlichem Ausgang, Strahlentherapie **64**:267-290 (Feb.) 1939.

1 case of malignant bronchial adenoma (case 6), a tumor of borderline malignancy and slow growth. In this instance the patient lived for forty-eight months, and even then the tumor was not very large, the patient dying of lobar pneumonia. If this case is excluded, the average duration of survival for the series treated by irradiation was ten and one-tenth months. 2. The control series contained many instances of primary cancer of the lung in which the primary tumor was clinically silent or relatively silent until the last days of life, but in which the clinical picture was dominated by cerebral symptoms due to metastases. In this type of case survival after onset of symptoms is relatively short (four, five, four, four and three months in some of these cases). At this institution such cases are relatively common because of the large neurosurgical service. Cerebral lesions of this type were not common in the series in which irradiation was used, because in this series the dominant clinical picture of pulmonary neoplasm led to the irradiation therapy. 3. The average period of survival after the first roentgen treatment was given was only one hundred and twelve and seven-tenths days if the case of malignant bronchial adenoma (case 6) is excluded.

It is perhaps unfair to include all of the cases in calculating the influence of irradiation on survival, because in many instances the treatment was given for palliation, with no hope of cure. If one may assume that only when the larger doses were given was an attempt being made to eradicate the tumor, one should properly use only these cases in studying the effects of irradiation on longevity. The patients in cases 1 to 5 (table 1), who received a depth dose of over 3,000 r, had an average survival period of twelve and four-tenths months after the onset of symptoms and one hundred and thirty-one and four-tenths days after the first roentgen treatment was given. The patients in cases 7 to 14 (table 2), who received depth doses between 1,000 and 2,000 r, had an average survival period of nine and five-tenths months from the onset of symptoms and seventy-six and seven-tenths days after the first roentgen treatment. It appears, then, that a vigorous attempt at cure was not particularly effective in prolonging life.

Since this study is based on postmortem material, it is clear that conclusions as to survival and cure following therapy must be made with caution. Cases of complete cure would not be included in a series of this kind. Cures would, however, be detected in a study such as that of Bloch and Bogardus.[1] They found none, and their data with respect to longevity correspond closely to those presented here.

There is disagreement in the reports in the literature as to the effectiveness of irradiation in prolonging life. This problem has been reviewed at great length by Simons.[7] Several important factors appear to have been neglected in many of the reported studies. These include failure to recognize the low degree of malignancy of some bronchial

tumors. Also, as far as I am aware, no one has studied in a large series of patients the period of survival *after the therapy was given* and compared it with a similar series in which irradiation was not used, calculating in this control series the period of survival from about the same time, namely, when the accurate diagnosis was first made.

The question of the palliative effects of irradiation therapy has not been discussed in this paper because the available data were considered inadequate.

SUMMARY AND CONCLUSIONS

In 21 cases of primary carcinoma of the lung, irradiation with tumor doses up to 5,000 r did not destroy the carcinoma as judged by histologic standards. The smallest dose which produced visible damage was 1,490 r, but the carcinocidal dose is probably above 5,000 r. In a metastatic carcinoma of the skull 3,800 r produced marked degenerative changes, apparently destroying the tumor cells, although the microscopic examination was not extensive enough to justify a final conclusion. Squamous cell carcinomas and adenocarcinomas of the lung were more radiosensitive than were the undifferentiated carcinomas which, contrary to their microscopic appearance, were either highly radioresistant or highly radiorecuperative. The histologic changes produced by irradiation consisted of degenerations, retrogressions or alterations in cell type and in tumor architecture, and they resembled those which have been described for other types of carcinoma. Undesired effects of irradiation on tissues and organs near the primary carcinomas were not seen. Survival was not notably prolonged by irradiation.

Most of the radiation therapy was given in the Radiation Clinic of the Division of Roentgenology, which supplied the technical data. Dr. David Tschetter gave valuable aid in the organization of the material. Dr. Cornelius Hospers granted permission for use of the postmortem data in case 4.

OSCILLOMETRIC READINGS IN CASES OF ARTERIOSCLEROTIC DISEASE OF THE LOWER EXTREMITY

SIGNIFICANCE AND INTERPRETATION

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Although oscillometry had previously found widespread use in Europe, it was not until 1927, when Samuels [1] popularized the method, that it began to be extensively used in the United States. Since then, numerous local articles have appeared [2] discussing the value of oscillometric readings in the study of peripheral arterial disease.

Before my observations concerning the significance and interpretation of oscillometric readings in cases of peripheral arteriosclerosis are presented, some of the well known physical principles on which arterial pulsation is based must be reviewed. When the left ventricle ejects a quantity of blood into the partially filled aorta, pressure changes are suddenly set up in the aorta and in the vessels at the root of the neck. These pressure changes are propagated along the branches of the arterial tree in the form of a wave moving at a speed computed to be eighteen to thirty times as fast as that at which the blood stream moves.[3] It is this pressure wave which constitutes the pulse, and it is the magnitude of the wave in a segment of an extremity which the oscillometer (with less than 100 per cent accuracy [3]) measures. As the pulse wave passes

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1. Samuels, S. S.: The Value of Oscillometry in the Study of Circulatory Disturbances of the Extremities, J. A. M. A. **88**:1780 (June 4) 1927.

2. Silbert, S., and Samuels, S. S.: Thromboangiitis Obliterans: Prognostic Value of the Oscillometer, J. A. M. A. **90**:831 (March 17) 1928. Kramer, D. W.: Evaluation of Various Methods of Investigating the Circulation in the Lower Extremities, Am. J. M. Sc. **185**:402 (March) 1933. de Takáts, G.; Hick, F. K., and Coulter, J. S.: Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, J. A. M. A. **108**:1951 (June 5) 1937. de Takáts, G.: Effect of Sympathectomy on Peripheral Vascular Disease, Surgery **2**:46 (July) 1937. Theis, F. V.: Popliteal Aneurysms as a Cause of Peripheral Circulatory Disease, with a Special Study of Oscillomographs as an Aid to Diagnosis, ibid. **2**:327 (Sept.) 1937. Ochsner, A., and DeBakey, M.: The Rational Consideration of Peripheral Vascular Disease, J. A. M. A. **112**:230 (Jan. 21) 1939. Gardner, C. E.: An Instrument to Measure Arterial Pulsation in the Digits, Surg., Gynec. & Obst. **69**:103 (July) 1939.

3. Wiggers, C. J.: Circulation in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1937.

along the arterial tree it gradually becomes "dampened out," so that by the time it reaches the arterioles it has disappeared. As a consequence, there is progressive diminution in the magnitude of arterial pulsation from the proximal to the distal end of an extremity.

There are several reasons for this "dampening out" process, two of the most important being that the arterial tree breaks up into progressively smaller and smaller branches and that, as it does so, a change occurs in the character of the vessel wall. There are a decrease in elastic tissue and a concomitant increase in smooth muscle which are under the influence of a greater or lesser degree of vasoconstrictor tone. By the time the arterioles are reached, there exists for all intents and purposes a system of inelastic tubes, the caliber of which is under the control of nervous, chemical and thermal influences. Without an elastic vessel wall there can be no pulsation. In other words, the existence of arterial pulsation depends on a sudden change in intra-aortic pressure which is propagated to the periphery in the form of a pulsatile wave only because the arterial wall is capable of passive stretching. Thus, arterial pulsation is, in a sense, a by-product of the peculiar structural and functional constitution of the circulatory system, subserving no particular function.

With this preliminary résumé as a background, it is possible to consider the significance and interpretation of oscillometric readings in cases of peripheral arteriosclerosis. First, as to their value in judging the effects of therapy: To give unequivocal information concerning the effects of treatment an instrument must be capable of either directly or indirectly measuring changes in the volume rate of blood flow through the diseased extremity. As has been seen, the oscillometer measures the magnitude of arterial pulsation in a segment of an extremity. The question arises concerning the relation existing between changes in volume rate of blood flow through an extremity and the magnitude of arterial pulsation in it.

Volume rate of blood flow through an extremity is increased chiefly by a decrease in the peripheral resistance brought about by dilatation of the peripheral arteriolar-capillary bed. To accommodate the increased flow of blood there also occurs normally an increase in the caliber of the main arterial trunks. By virtue of this increase in caliber and the concomitant increase in elasticity of the vessel walls through diminution of their tonus, less dampening of the pulse wave occurs; hence there is an increase in the magnitude of pulsation.

However, in the presence of arteriosclerotic disease in which the elasticity of the vessel walls has been impaired, a wide variation in the volume rate of blood flow through the partially occluded vessels occurs without any corresponding change in the caliber or elasticity of the vessels or, consequently, in the magnitude of their pulsation. In addition, since a collateral circulation consists of a network of very fine

vessels, the pulse wave may be completely dampened out by the small caliber of these vessels. A patient with complete occlusion of the main arterial trunks may thus have an effective collateral circulation and still present no detectable pulsation. It is for these reasons that oscillometry is of little, if any, value in judging the effects of treatment of peripheral arteriosclerotic disease. I have records of over 50 patients with peripheral arteriosclerotic disease who have obtained definite benefit from various forms of therapy, as evidenced by relief of symptoms and healing of ischemic lesions, without any change in the oscillometric readings.

If oscillometry gives no information concerning the volume rate of blood flow through arteriosclerotic extremities, what is its practical value in the diagnosis of this disease? Since arteriosclerotic disease destroys or impairs the elasticity of the arterial walls, sclerotic arteries either do not pulsate at all or pulsate less than they should, and it was hoped that oscillometry would reveal these decreases in pulsation. Estimation of pulsation in the leg by palpation of the dorsalis pedis and posterior tibial arteries is a crude and inaccurate method. Many patients are seen in whom no pulsation can be detected in either of these arteries, and yet the oscillometer reveals a surprisingly large amount of pulsation in the lower part of the leg. The converse of this is also true, that patients with a degree of arteriosclerotic disease sufficient to produce symptoms may still exhibit palpable pulsation in all the peripheral arteries. It is not sufficiently appreciated that the cold, pulseless foot which blanches on elevation represents a very advanced stage of arteriosclerotic disease. The patient with early involvement may present no objective evidence of the true cause of his symptoms, and it is not unusual to see such a patient treated for a multiplicity of disorders, such as varicose veins, flat feet and rheumatism, until physical findings characteristic of arterial disease make their appearance. It is for this type of patient that a method capable of revealing decreases in arterial pulsation, inferentially due to early arteriosclerotic disease, would be a distinctly valuable diagnostic adjunct. Yet it was with this very type, for which the information was most needed, that the oscillometer proved in my hands to be most disappointing. If the significance of a blood pressure reading is compared with that of an oscillometric reading, the reason becomes apparent. Certain norms have been established for blood pressure readings when a given technic is used; but there is no such thing as a normal oscillometric reading for any given level of an extremity. For example, oscillometric readings taken at the level of the lower part of the leg in persons with normal arteries range between 1 and 10; yet, as will be shown, readings obtained at this level in cases of sclerotic disease often fell somewhere within this range. In other words, an oscillometric reading normal for one person can be grossly subnormal for another.

The problem was to find some simple way of determining whether an oscillometric reading in a case of suspected arteriosclerotic disease of a lower extremity, irrespective of its absolute magnitude, represented a decrease in arterial pulsation. In a recent article [4] a preliminary report of a new method of applying oscillometry to the diagnosis of arteriosclerotic disease of the lower extremity was presented. Considerable experience with it leads me to believe that it is the answer to the aforementioned difficulties.

Since peripheral arteriosclerotic disease involves the lower extremities to a much greater extent than the upper, it follows that as the disease progresses oscillometric readings taken at any given level in the lower extremities should decrease proportionately more than those at any given level in the upper extremities. To test this hypothesis, a series of oscillometric readings for the lower part of the leg and for the distal third of the corresponding forearm in active young adults free of vascular disease were recorded to establish the ratio that exists normally between oscillometric readings at these two levels. The lower edge of the cuff was placed at the base of the internal malleolus and at the wrist joint. The lower part of the leg was chosen because, with the exception of certain types of pain involving the calf, arteriosclerotic disease of the lower extremity usually manifests itself at or distal to this level. Consequently, information revealing a decrease in arterial pulsation in this segment is particularly significant. In a series of ninety ratios thus obtained, in which the reading at the lower part of the leg was used as the numerator, the lowest ratio was 1. This means that in active adults free of vascular disease the magnitude of arterial pulsation in the lower part of the leg is at least equal to that in the lower part of the forearm.

Therefore, assuming the correctness of the original premise that as peripheral arteriosclerotic disease progresses oscillometric readings taken at any given level in the lower extremities decrease proportionately more than those taken at any given level in the upper extremities, a point should be reached in the course of the disease at which the magnitude of arterial pulsation in the lower part of the leg becomes less than that in the lower part of the forearm and the ratio less than 1. During the past two years this ratio has been computed in every case in which a diagnosis of peripheral arteriosclerotic disease could be made from physical examination. All the patients have been ambulatory. At present over one hundred such determinations have been made, and in every instance the ratio obtained has been less than 1. In approximately 50 per cent the oscillometric reading at the lower part of the leg was 1 or higher despite the fact that in no case could pulsation be palpated

4. Atlas, L. N.: Oscillometry in the Diagnosis of Arteriosclerosis of the Lower Extremities: A New Method of Application, Arch. Int. Med. **63**:1158 (June) 1939.

TABLE 1.—*"Normal" Oscillometric Readings at the Level of the Lower Part of the Leg in the Presence of Arteriosclerotic Disease with Absence of the Pedal Pulses* *

Lower Part of Leg	Lower Part of Forearm	Ratio
1.0	7.5	0.1
1.0	5.0	0.2
1.5	7.5	0.2
1.0	3.0	0.3
1.5	5.0	0.3
2.0	6.5	0.3
1.0	2.5	0.4
1.5	3.5	0.4
3.5	8.0	0.4
1.0	2.0	0.5
1.5	3.0	0.5
2.5	5.0	0.5
4.0	8.0	0.5
2.0	3.5	0.6

* The actual subnormality of these readings is indicated by their ratio to readings taken at the level of the lower part of the forearm.

TABLE 2.—*Instances of Excellent Pulsation at the Level of the Lower Part of the Forearm in the Presence of Advanced Arteriosclerotic Disease of the Lower Extremity*

Pulsation in Lower Part of Leg	Pulsation in Lower Part of Forearm	Ratio
0	5.0	0
0	4.5	0
0	3.0	0
Trace	6.5	0
Trace	4.0	0
Trace	3.5	0

TABLE 3.—*Comparison of Oscillometric Readings for the Lower Part of the Leg with Readings for the Lower Part of the Forearm in Persons with Early Arteriosclerotic Disease of the Lower Extremity* *

		Palpable Pulse		Oscillometric Readings		
Age	Symptoms	Dorsalis Pedis Artery	Posterior Tibial Artery	Leg (Lower Part)	Forearm (Lower Part)	Ratio
55	Intermittent claudication; cold foot.....	Yes	No	1.0	5.0	0.2
66	Intermittent claudication; numb foot.....	Yes	No	1.0	4.0	0.25
56	Intermittent claudication frustrans.....	Yes	Yes	1.0	4.0	0.25
53	Intermittent claudication; cold, numb foot	Yes	No	2.0	4.0	0.5
68	Cramps in leg; cold, numb foot.....	Yes	No	4.0	7.5	0.5
62	Intermittent claudication; cold foot.....	Yes	Yes	2.5	4.0	0.6
66	Intermittent claudication; numb foot.....	Yes	No	2.5	4.0	0.6
55	Intermittent claudication; cold foot.....	Yes	Yes	2.5	4.0	0.6
58	Painful, cold, numb foot.....	Yes	No	2.5	3.5	0.7
53	Intermittent claudication; cold, numb foot	Yes	No	3.0	4.5	0.7
58	Painful, cold, numb foot.....	Yes	Yes	3.5	4.5	0.7

* Note the characteristic symptoms, the presence of palpable pulsation in the pedal arteries, the oscillometric readings for the level of the lower part of the leg within the "normal" range and the ratios below 1.

in the dorsalis pedis or the posterior tibial arteries (table 1). Without this method of comparison, such readings would fall within what is considered to be the normal range for oscillometric readings taken at the lower part of the leg. Table 2 illustrates the relative freedom of the upper extremity from arterial involvement in the presence of advanced arteriosclerotic disease of the lower extremity.

This ratio has been computed also in another group of cases, which in many respects is more interesting. In this group, although the symptoms of peripheral arteriosclerotic disease were characteristic, the diagnosis could not be made from physical examination alone. Color changes, trophic changes or other objective evidence of diminished circulation were absent. In every instance some pulsation could be detected in the dorsalis pedis artery, and in some instances there was pulsation in the posterior tibial artery as well. These cases represent as early a stage of peripheral arteriosclerotic disease as one sees clinically (table 3).

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RELATION BETWEEN MULTIPLE PERIPHERAL NEUROPATHY AND CIRRHOSIS OF THE LIVER

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Rolleston and McNee,[1] in their splendid book on diseases of the liver, gallbladder and bile ducts, stated:

> The minor degrees of peripheral neuritis are often thrown into the shade by ascites or other effects of cirrhosis on which attention is focused, and so pass undetected. Cramps, muscular tenderness and loss of the tendo Achilles and knee jerks may occur in cases of cirrhosis admitted for ascites or hematemesis, and are, generally speaking, to be referred to alcoholism. Peripheral neuritis in the early stages of cirrhosis is usually alcoholic; it may be due to a combination in varying degrees of alcoholism and hepatic insufficiency.

It is the purpose of this paper to examine the connection between peripheral neuropathy (to use the term proposed by Wechsler [2] to replace peripheral neuritis) and hepatic cirrhosis in the light of the evidence which has recently been given on the etiology of the former condition and to present our own statistics on the subject.

A moving account of the rapid development of coexisting peripheral neuropathy and cirrhosis of the liver in a 30 year old alcoholic woman was reported by Lancereaux [3] in 1865. In 1896 Gouget [4] reported the case of a woman who was admitted to the hospital for cirrhosis of the liver. On entry she stated that she had cramps in the calves. Within two months she had severe neuropathy involving the motor and sensory portions of the nerves of both extremities. The neuropathy was proved at autopsy two weeks later. According to Gouget, the source of the

From the Department of Medicine, Stanford University, and the Department of Public Health, City and County of San Francisco.

1. Rolleston, H., and McNee, J. W.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 314.

2. Wechsler, I. S.: Multiple Peripheral Neuropathy Versus Multiple Neuritis, J. A. M. A. **110**:1910-1913 (June 4) 1938.

3. Lancereaux, E.: Studies on Alterations Produced by the Abuse of Alcoholic Beverage, Gaz. hebd. de méd. et de chir. **2**:435-439 (July 14) 1865.

4. Gouget, A.: Hepatic Insufficiency and Peripheral Neuritis, Rev. de méd. **17**:537-546 (July) 1897.

nerve lesion was hepatic insufficiency. By 1904 Sainton and Castaigne [5] had collected 7 other cases, including 2 of their own. In 1907 Guillaumot [6] was able to find 18 cases.

In 1908 Klippel and Lhermitte [7] summarized the French literature up to that time in an excellent article in which they reported 3 personal cases and analyzed the problem from the clinical, pathologic and etiologic points of view. They recognized two types of neuropathy, one appearing as a terminal phenomenon in moribund persons with cirrhosis, the other occurring distinctly earlier in the disease. The former they associated with cachexia and malnutrition and considered a degenerative process associated with toxic products of cachexia. They stated that alcohol need not be connected with this type of neuropathy. The more common type of polyneuritis they found in conjunction with a large liver and marked alcoholism, usually in women between the ages of 30 and 40. They concluded that this type of neuritis (which they labeled definitely inflammatory) is not essentially different from that occurring in persons with alcoholic polyneuritis uncomplicated by cirrhosis. The fact that the polyneuritis was often severe was attributed to the circumstance that the hepatic disease lowered the antitoxic function of the liver, so that the noxious properties of alcohol (or of some substance contained in the spirits consumed) were not neutralized and could work freely on the tissues of the nervous system.

Rolleston and Fenton [8] reported the necropsy observations in 114 cases of cirrhosis in 1896. In 3 cases (in all of which the patients were females) death was considered due to the alcoholic neuritis which developed late in the course of the disease. Candler [9] found 4 of 82 deaths due to neuritis.

A few years later Eppinger and Arnstein [10] remarked that polyneuritis probably occurs more often in connection with disease of the liver than one would suspect from the literature. They reported 6 cases of neuritis, in 2 of which the patients were obviously cirrhotic (1 a nonalcoholic patient). The other 4 had disturbances of hepatic physiology as judged by tests of hepatic function; 2 of these had large livers.

5. Sainton, P., and Castaigne, J.: Coexistence of Alcoholic Cirrhosis and Peripheral Neuritis, Arch. gén. de méd. **2**:2446-2455, 1904.

6. Guillaumot, H. L., cited by Klippel and Lhermitte.[7]

7. Klippel, M., and Lhermitte, J.: Neuritis in the Course of Cirrhosis of the Liver, Semaine méd. **28**:13-17 (Jan. 8) 1908.

8. Rolleston, H., and Fenton, W. J.: On the Cirrhotic Liver, Birmingham M. Rev. **40**:193-215, 1896.

9. Candler, J. P.: A Comparative Inquiry into the Incidence of Cirrhosis of the Liver at Charing Cross Hospital and Claybury Asylums, Arch. Neurol., Claybury **3**:441-446, 1907.

10. Eppinger, H., and Arnstein, A.: On the Pathogenesis of Polyneuritis, Ztschr. f. klin. Med. **74**:324-333, 1912.

In all cases the nerve involvement was severe and was the reason for hospitalization.

In more recent years the subject of neuropathy in connection with cirrhosis has been comparatively neglected. In his textbook on diseases of the liver, published in 1935, Weiss [11] mentioned only that "cirrhotic patients are frequently attacked by neuritis particularly when alcoholic paralysis is located in the lower extremities." In his authoritative book published in 1937, Eppinger [12] stated that polyneuritis occurs in 3 per cent of persons with cirrhosis. Individual cases have been reported by Barker [13] and by Meyers.[14]

Mancke [15] considered peripheral nerve changes rarer in cirrhosis than in metabolic diseases, such as diabetes. He reported 5 cases in which there was isolated absence of the knee and ankle jerks; 1 of these was a case of pigmentary cirrhosis (previously reported by Nakano [16]), 1 was a case of cirrhosis associated with diabetes and 3 were cases of pigmentary cirrhosis with diabetes.

With regard to etiology, Rolleston and McNee [1] summed up general opinion in 1929:

> The terminal stages of cirrhosis are marked by symptoms due to hepatic insufficiency, such as epistaxis and other hemorrhages, delirium and coma. The toxic coefficient of the urine will, if the kidneys be healthy, become increased as a result of the liver failing in its antitoxic function, and a toxemic neuritis may result. If alcohol has been taken recently, the neuritis must be considered to be due to this cause, but in the absence of this factor hepatic insufficiency with resulting toxemia is a satisfactory explanation. Very little alcohol may cause neuritis in advanced cirrhosis.

These views combine those of Klippel and Lhermitte [7] and those of Gouget,[4] expressed many years before.

Eppinger and Arnstein [10] concluded that a toxin retained in the liver or one unchanged by the intestine might be responsible for the development of neuritis or that the hepatic insufficiency and polyneuritis might both be the result of a third factor. They suggested that this hypothetic factor might be a fluorescent substance, such as hematoporphyrin.

The conception of peripheral neuropathy as the result of vitamin B deficiency has now been established on a sound footing. The role of

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11. Weiss, S.: Diseases of the Liver, Gall Bladder, Ducts and Pancreas: Their Diagnosis and Treatment, New York, Paul B. Hoeber, Inc., 1935, p. 412.

12. Eppinger, H.: Die Leberkrankheiten, Berlin, Julius Springer, 1937.

13. Barker, L. F.: Chronic Alcoholism with Cirrhosis Hepatitis, Polyneuritis and Personality Disorder, Internat. Clin. **1**:17-35 (March) 1929.

14. Meyers, F. M.: Conditioned Deficiency Especially in Cirrhosis of the Liver, Geneesk, tijdschr. v. Nederl-Indië **77**:1155-1162, 1937.

15. Mancke, R.: Peripheral Neuritis in Pigmentary Cirrhosis, Deutsche Ztschr. f. Nervenh. **125**:279-285, 1932.

16. Nakano, J.: Hemachromatosis Resembling Addison's Disease, München. med. Wchnschr. **61**:919-923 (April 28) 1914.

alcohol as a direct toxic agent was ruled out by Strauss[17] and by Blankenhorn and Spies.[18] Jolliffe and his collaborators[19] have successfully treated a large number of patients with peripheral neuropathy with crystalline vitamin B_1 and with concentrates of the vitamin B complex.

Goodhart and Jolliffe[19a] included several cases of cirrhosis of the liver in their study on the effects of vitamin B therapy on the polyneuritis of alcoholic addicts. They obtained improvement in the neuropathy and also in the general condition of the patient.

The following series represents a summary of cases in which the patients were admitted to the Stanford Medical Service of the San Francisco County Hospital and discharged with a diagnosis of cirrhosis of the liver. The records reviewed cover the period from July 1, 1928, to Jan. 1, 1939. There are included a total of 272 patients, with 317 entries. Readmissions for abdominal paracenteses and most other causes were excluded. However, readmissions because of a flare-up in the hepatic process were considered fairly within the province of this thesis and were included. The intervals between admissions in these cases varied from a few months to eight years. There was liable to be a diagnosis of neuritis on one admission and not on another. As may be seen (table 2), the percentage of readmissions among the patients with neuropathy was nearly the same as among those without it. In most of the cases the diagnosis of peripheral neuropathy was not the primary one.

Care was taken to eliminate so-called fatty alcoholic livers with peripheral neuropathy. The criteria used were: (1) the pathologist's diagnosis in case of death; (2) laboratory tests, including the retention of bromsulphalein dye, the Takata reaction and the degree of anemia; (3) the history; (4) the physical signs, including the development of ascites, the collateral circulation and the presence or absence of gastrointestinal hemorrhage, and (5) the course under subsequent observation. Use was made of these same criteria in an attempt to grade cirrhosis in three stages—early, moderately advanced and far advanced.

The criteria used for the diagnosis of peripheral neuropathy were a history of pain, burning, numbness or weakness in the limbs, paresthesia, tenderness of the calves, paresis, paralysis and atrophy of muscles and

17. Strauss, M. B.: The Etiology of "Alcoholic" Polyneuritis, Am. J. M. Sc. **189**:378-382 (March) 1935.

18. Blankenhorn, M. A., and Spies, T. D.: Prevention, Treatment and Possible Nature of the Peripheral Neuritis Associated with Pellagra and Chronic Alcoholism, Tr. A. Am. Physicians **50**:164-166, 1935.

19. (*a*) Goodhart, R., and Jolliffe, N.: Effects of Vitamin B (B_1) Therapy on the Polyneuritis of Alcohol Addicts, J. A. M. A. **110**:414-418 (Feb. 5) 1938. (*b*) Jolliffe, N., and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, ibid. **107**:642-647 (Aug. 29) 1936.

alterations of the patellar and ankle tendon reflexes. No one sign alone was taken as diagnostic. In the majority of the cases there was no more than tenderness of the calves, absent ankle jerks, edema of the dorsa of the feet and wasting of muscles. It is to be emphasized that this series includes a large percentage of cases of mild multiple peripheral neuropathy as well as a few cases of severe involvement of the type which most previous authors have reported.

The following case is presented as an illustration.

REPORT OF A CASE

E. J., a woman aged 44, was admitted to the hospital Feb. 4, 1938. She had first been admitted to the San Francisco Hospital in 1930, complaining of nausea, vomiting and anorexia. Her condition was then diagnosed as cirrhosis of the liver, chronic alcoholism and syphilis. At that time there was no jaundice or enlargement of the abdomen. She had mild peripheral neuropathy and tenderness of the liver. Her second entry was in 1933, for alcoholism and a flare-up of hepatitis. There was no icterus. No spider hemangiomas were present, and there was no peripheral neuropathy. The liver was palpable 15 cm. below the right costal margin; it was slightly tender and not hard. The complaints were again of nausea and vomiting. No ascites was recorded. Mild anemia was present on both entries.

On her third entry (the present) there had been six months of progressive weakness, epigastric discomfort, attacks of nausea and gagging. Recently she had been unable to walk. Soreness of the legs, numbness of the hands and enlargement of the abdomen had developed.

Physical Examination.—The patient was dull, apathetic and stupid appearing, with wasted muscles and a large, fluid-containing abdomen. Spider hemangiomas were present. There was no icterus. The liver was palpable 4 cm. below the right costal margin and was hard and tender. The teeth were in bad condition. There were tenderness over the calves and marked weakness of the hands and legs. The tendon reflexes were absent.

Laboratory Data.—The value for hemoglobin was 70 per cent. There were 3,470,000 red cells and 14,400 white cells per cubic millimeter of blood. There were 74 per cent neutrophils. The sedimentation rate was 42 mm. in one hour. The mean corpuscular volume was 109. The Takata reaction was 00110000 in the blood and 01100000 in the ascitic fluid. The value for serum protein was 6.8; globulin 4.2. The icterus index was 9. The value for blood urea was 22 mg. per hundred cubic centimeters. There was no urobilin or bile in the urine. The Wasserman reaction was negative. The protein content of the spinal fluid was 50. The Pandy test showed a faint trace of globulin. The Wassermann reaction was negative. The Lange curve was 1111221100.

Course.—The patient was kept one month in the hospital under the routine ward regimen, without change except that she became unable to walk. Beginning on March 7, she was placed on a high vitamin, high carbohydrate, low fat diet and given 6.6 mg. of thiamine chloride daily. From this time on she showed gradual but steady improvement. After four weeks she was much more wide awake and mentally clear, had a fairly decent appetite, was beginning to gain weight and had softer skin. She still showed numbness of the hands. The dose was raised to 13.2 mg. daily on April 4. The improvement in her condition was

accelerated. She was discharged on April 22 "feeling better than she had in years." The appetite was excellent; the skin was velvety. There was no evidence of ascites. The liver was down 5 cm. There was no tenderness in the calves. Strength was improved in both hands. She was walking freely and helping make beds. The value for hemoglobin was 82 per cent. There were 4,030,000 red blood cells per cubic millimeter. The mean corpuscular volume was 96.7. The Takata reaction was 00000000.

Summary.—This was a case of moderately advanced cirrhosis of the liver and multiple peripheral neuropathy with at least three flare-ups of hepatitis. Improvement followed administration of a high vitamin, high carbohydrate diet and of

TABLE 1.—*Summary of All Admissions for Cirrhosis of the Liver from July 1928 to January 1939*

	Number	Per Cent
Entries	317	..
Cases	272	..
Sex		
Males	183	58
Females	134	42
Stage		
Advanced	168	53
Moderate	87	27
Early	62	20
Mortality		
Per entry	149	47
Per case	149	55
Signs		
Neuropathy	55	17
Large liver	235	74
Ascites	203	64
Jaundice	182	58
Gastrointestinal hemorrhage	110	35
Weakness	179	56
Associated conditions		
Pellagra	10	3
Deficient diet	72	23
Alcoholism	230	72
Laboratory data		
Takata reaction obtained	148	47
Positive Takata reaction	110	74
Hemoglobin estimated	296	96
Hemoglobin under 70% (Sahli)	143	48

thiamine chloride. The rate of improvement accelerated when the dose was doubled. During the course of treatment the macrocytic anemia diminished and precipitation in the Takata reaction disappeared.

COMMENT

In table 1 are summarized a number of facts which indicate the condition of the patient with regard to various aspects of cirrhosis other than peripheral neuropathy: males were more common than females, in a ratio of about 6 to 4. In four fifths of the patients the condition was regarded as far advanced or moderately advanced.

With regard to specific diagnostic symptoms and signs, one third of the patients had had hemorrhage from the gastrointestinal tract; over one half had weakness as an outstanding complaint. Six of 10 had a lesser or greater degree of jaundice (jaundice in these patients means either distinct clinical jaundice or an icterus index of 12 or more).

The liver was considered large in three fourths. Anemia, as gaged by a hemoglobin content of below 70 per cent (Sahli), was found in one half. The Takata test was performed as a routine procedure on over one half. In 74 per cent the reaction was positive—a lower percentage of positive Takata reactions in cases of cirrhosis of the liver than was found by us previously but fitting in with general experience when the test has been done routinely.[20]

TABLE 2.—*Analysis and Comparison of Data on Entries for Cirrhosis With and Without Peripheral Neuropathy from July 1928 to January 1939*

	Cirrhosis with Peripheral Neuropathy		Cirrhosis Without Peripheral Neuropathy	
	Number	Per Cent	Number	Per Cent
Entries	55	..	262	..
Cases	48	87	224	85
Sex				
Males	20	36	163	62
Females	35	64	99	38
Stage				
Advanced	24	44	144	55
Moderate	14	25	73	28
Early	17	31	45	17
Mortality				
Per entry	24	44	125	48
Per case	24	50	125	56
Signs				
Large liver	47	86	188	72
Ascites	31	56	172	66
Jaundice	31	56	151	58
Gastrointestinal hemorrhage	17	31	93	36
Weakness	38	69	141	54
Associated conditions				
Alcoholism	50	91	180	69
Deficient diet	22	40	51	20
Pellagra	4	7	6	2
Laboratory data				
Positive Takata reaction	26	72	84	75
Hemoglobin under 70% (Sahli)	23	50	120	48

A history of alcoholism was noted in more than 70 per cent of cases. Pellagra was present in 3 per cent. A deficient diet was admitted in 23 per cent. The mortality by entry was 47 per cent. The mortality by case was 54 per cent.

Peripheral neuropathy was diagnosed in 55 of the 317 entries, or 17 per cent (table 2). If the figures in the cases in which peripheral neuropathy was present are compared with those in which it was not diagnosed, certain differences are found. In the group of patients with neuropathy there was a reversal of the sex ratio, 64 per cent being female as opposed to 38 per cent of the remaining patients. The per-

20. Wayburn, E., and Cherry, C. B.: The Takata Reaction in the Blood Serum, Am. J. Digest. Dis. **5**:231-238 (June) 1938.

centage of cases in which the cirrhosis was graded as "early" was greater in the group with neuropathy, being 31 per cent as opposed to 17 per cent in those without nerve involvement. In line with this was a lower incidence of gastrointestinal hemorrhage and ascites. The occurrence of a large liver was slightly more frequent. The complaint of weakness was more obvious (69 per cent as compared to 54 per cent). The mortality rate was lower. The average age was several years less for the patients with neuropathy. The incidence of alcoholism, of admitted dietary deficiency and of pellagra was markedly increased in this group. Ninety-one per cent of the patients with neuropathy admitted alcoholism, as opposed to 69 per cent of those without neuropathy. Forty per cent

TABLE 3.—*Increased Incidence of Cirrhosis of the Liver with Peripheral Neuropathy (July 1928 to January 1939)*

Year	Total Admissions*	Total Entries for Cirrhosis, Number	Entries for Cirrhosis and Peripheral Neuropathy	
			Number	Per Cent
1928 (6 mo.)	548	8	0	0
1929	1,098	13	0	0
1930	1,223	16	2	12
1931	1,294	13	0	0
1932	1,262	21	2	10
1933	1,289	31	4	13
1934	1,177	27	1	4
1935	1,158	32	5	16
1936	1,357	61	13	21
1937	1,406	46	6	13
1938	1,357	49	22	45
Total	13,169	317	55	17

* All figures refer to admissions to the general medical service (Stanford University) of the San Francisco Hospital. The only figures available for total admissions are scheduled on the fiscal year (July to July). To reach the figures listed, the total for each fiscal year has been halved and the resulting half combined with the total for half the succeeding year.

with nerve lesions admitted having taken an inadequate diet, while a similar history was obtained in only 20 per cent of the remaining cases. Finally, 7 per cent of the cirrhotic patients with multiple neuropathy had associated pellagra, whereas only 2 per cent of those without the former deficiency disease had the latter one.

If the figures are broken down and the entries recorded by years (table 3), two important statistical facts become apparent. First, there has been a marked increase in the number of patients with cirrhosis of the liver admitted to the San Francisco Hospital since 1933, which has been even more accentuated since 1936. Second, there seems to have been a tremendous rise in the incidence of coexisting multiple peripheral neuropathy and cirrhosis. However, the latter change coincides with the appearance of a personal interest in this problem, with the result that patients with cirrhosis have been more carefully investigated. Prior to this only a high grade of neuropathy was thought worthy of note.

If the neuropathy was mild, if the patient had been recently drinking or if the neurologic signs cleared during the stay in the hospital, the neuropathy was liable to be overlooked. The recorded incidence of over 45 per cent of the 49 cases of cirrhosis observed in 1938 is considered by us much closer to the true situation than the 7 per cent recorded in 129 admissions for the years 1928 to 1934.

Evaluation of Therapy.—An attempt has been made to evaluate the therapy of patients having cirrhosis with multiple peripheral neuropathy. High vitamin diets, liver extract [21] and various preparations of vitamin B were used. Vitamin B concentrates (brewer's yeast and wheat germ extract) were given in doses ranging from 1,000 to 4,000 international units (of thiamine) daily. Thiamine chloride [21] was administered orally or parenterally in amounts varying from 5 to 60 mg. daily. Treatment was usually begun after a control period and continued throughout the stay in the hospital.

In 24 of the cases of cirrhosis complicated by peripheral neuropathy the patients were in the terminal stage of cirrhosis. Large doses of thiamine chloride (up to 60 mg. daily) were given parenterally to 4 of these patients without any demonstrable effect on either the cirrhosis or the neuropathy.

Among the 31 who survived, 6 were treated with high vitamin diets and liver extract. Ten others received, in addition, vitamin B concentrates with or without thiamine chloride. Four of the 6 patients receiving the former, and all of the 10 patients receiving the latter treatment showed clearing of their subjective and objective neurologic symptoms during their residence in the hospital (a matter of a few weeks in most instances).

Clearing of neurologic signs also occurred in a certain number of patients who received no therapy other than the regular hospital diet (which has a vitamin content above the average). Of 15 such patients in this series, 9 showed eventual improvement. The regression of signs seemed to occur more rapidly in the adequately treated patients. In only a few was it dramatic.

COMMENT

The occurrence of multiple peripheral neuropathy in such a high percentage of cases of cirrhosis of the liver seems a fact of importance. The increase in the amount of hepatic cirrhosis itself seen at this hospital in the past few years is marked. This, as well as the apparent startling rise in the percentage of cirrhotic persons who have the complication of peripheral neuropathy, is probably related to the increase in admissions of patients with alcoholism to the hospital. Another factor in the

21. Eli Lilly & Co. supplied generous amounts of thiamine chloride (betalin S) and liver extract.

apparent increase in neuropathy, as has been pointed out earlier, is awareness of the problem.

Early cirrhosis was seen more often in the group of patients having peripheral neuropathy, for several reasons. The neuropathy itself may have been the patient's chief complaint. It may have imposed an additional set of symptoms, i. e., just enough more to make the patient seek medical aid. Or it may have been associated with another syndrome, such as some other deficiency disease, acute alcoholism or postalcoholic gastritis.

The observation that cirrhosis accompanied by peripheral neuropathy is more common in females whereas cirrhosis alone is found predominantly in males is an interesting although as yet unexplained observation which has been noted by others [1] as well as ourselves.

The connection between peripheral neuropathy and cirrhosis may help in throwing light on the etiology of the latter condition. There are associated, in too high a percentage incidence to be coincidental, two diseases, one with and one without known etiologic factors. If peripheral neuropathy may be regarded as a fairly reliable sign of deficiency of vitamin B_1, the obvious inference is that there is in cases of cirrhosis a deficiency of thiamine. It does not follow that thiamine deficiency is the cause of hepatitis or that thiamine protects the liver from injury. We are at present investigating the effect of thiamine in cases of experimental damage to the liver.[22]

It is becoming increasingly apparent that vitamin deficiencies rarely occur singly. This may be said particularly of the various members of the so-called vitamin B complex. Although the increased incidence of pellagra is the only aspect of such deficiency offered statistically in this paper, we have not infrequently observed other types of deficiency disease in patients with cirrhosis of the liver. Jolliffe,[19a] Patek [23] and we have observed clinical improvement in the general well-being of cirrhotic patients at the same time that their neuropathy regressed under treatment with large doses of vitamin B. It is possible that the vitamin B complex may contain a liver-protective factor. György and Goldblatt [24] kept a colony of rats on a diet deficient in the vitamin B complex and supplemented by vitamin B_1 and B_6 and riboflavin. In 48 of these they observed changes in the liver, ranging from parenchymatous and fatty degeneration to cirrhosis. These changes could be prevented by the addition of yeast to the diet.

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22. Wayburn, E., and Cox, A. J.: Unpublished data.

23. Patek, A. J., Jr.: Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, Proc. Soc. Exper. Biol. & Med. **37**:329-330, 1937.

24. György, P., and Goldblatt, H.: Hepatic Injury on a Nutritional Basis in Rats, J. Exper. Med. **70**:185-192 (Aug.) 1939.

Rich and Hamilton [25] fed rabbits diets supplemented by various vitamins. Cirrhosis of the liver occurred in all of 14 rabbits the diets which lacked yeast. This cirrhosis resembled Laennec's cirrhosis in man. It was not prevented by the specific addition of vitamins B_1, $G(B_2)$, and B_6, and nicotine acid to the diet but was prevented by the addition of brewer's yeast.

Wilbur and Snell [26] have summarized the role of the gastrointestinal tract in the development of deficiency states as (1) the result of an inadequate intake of food due to anorexia or an incomplete diet; (2) the result of a loss of essential secretion or of food due to vomiting, diarrhea or external fistulas; (3) the result of a lack of decreased production of essential substances, and (4) the result of inadequate intestinal absorption. A lack of food intake by our patients seems undoubted. The failure of an alcoholic addict to admit this lack of proper nutrition is extraordinarily common, and it is small wonder that the incidence of allegedly poor diets as obtained in routine histories is as low as it is. It does seem noteworthy that the incidence of deficient diets was distinctly higher in those patients who had the complication of multiple peripheral neuropathy (although increased diligence on the part of the history taker may account for some of the difference). If one observes that which the patient actually eats, one reaches the conclusion that the overwhelming majority of patients entering this hospital with cirrhosis of the liver have been on a deficient diet. Whether it be cause or effect, many of those in the active stage have anorexia, nausea, "gas on the stomach" and vomiting. Some go on voluntary diets because of their gastrointestinal complaints; these diets usually are deficient in vitamins and proteins. Some have been drinking alcoholic liquors up to the hour of admission to the hospital. Others confess to the imbibition of inconsequential to tremendous amounts of these beverages in the past but sadly relate the cessation of such activity a few weeks or a few months previously because of the gastrointestinal symptoms which were produced. The direct toxic effect of alcohol as a factor in production of the peripheral neuropathy connected with cirrhosis thus appears to be ruled out, even as it has been ruled out under other circumstances.

Achlorhydria and hypochlorhydria are common in patients with cirrhosis. They are likewise commonly associated with various deficiency diseases. The significance of this or of possible decreased intestinal

25. Rich, A. R., and Hamilton, J. D.: The Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet, Bull. Johns Hopkins Hosp. **66**:185-196 (March) 1940.

26. Wilbur, D. L., and Snell, A. M.: Deficiency States Associated with Gastro-Intestinal Disease, Am. J. Digest. Dis. & Nutrition **4**:720-725 (Jan.) 1938.

absorption in cases of cirrhosis is difficult to evaluate. The same is true of the possibility that there is an inability on the part of the liver to metabolize thiamine adequately because of hepatic damage.

SUMMARY AND CONCLUSIONS

From an analysis of records of patients seen in the San Francisco County Hospital during the years 1928 to 1939 the following facts are noted:

Multiple peripheral neuropathy occurred in a high percentage of cases of cirrhosis of the liver.

There was a marked increase in the incidence of cirrhosis and probably of coexisting multiple peripheral neuropathy in the years 1933 to 1939.

A predominance of female patients and a higher percentage of early cirrhosis were observed in the cases in which neuropathy was present.

Alcoholism, general dietary deficiency and deficiency of thiamine intake were associated with both diseases.

The peripheral neuropathy of the patient with cirrhosis regressed when high vitamin therapy and, particularly, large amounts of vitamin B were administered.

The general condition of the patient with cirrhosis often improved at the same time.

Progress in Internal Medicine

BLOOD

REVIEW OF RECENT LITERATURE

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(Continued from page 1294)

GRANULOCYTOPENIA

A persual of the literature for 1939 dealing with granulocytopenia indicates that aminopyrine is now less important as an etiologic factor than it was several years ago. This is due to its decreased use, which undoubtedly is attributable to the knowledge that it may cause this serious condition. On the other hand, an increasing number of cases of granulocytopenia due to sulfanilamide and sulfapyridine are being reported. All evidence indicates that the most serious untoward effect of these two drugs is the production of granulocytopenia, which in a high percentage of the reported cases has terminated fatally. The exact incidence of granulocytopenia as a complication of sulfanilamide and sulfapyridine therapy is unknown, because doubtless many recognized cases are unreported, and in numerous others the syndrome is not identified. It apparently does not occur as frequently as the two other serious complications, namely, hemolytic anemia and gross hematuria resulting from deposition of crystals in the urinary tract. The granulocytopenia due to these substances does not appear to be associated with individual sensitivity of the person being treated but probably results from overdosage. A survey of the literature indicates that this complication rarely appears until a total of between 35 and 50 Gm. has been given; this amount is usually given over a period of twelve to fourteen days.

Observations in recent years have indicated clearly that gold preparations may cause granulocytopenia, but as such preparations have not been used extensively in the United States, their causal relation to the syndrome has not received widespread recognition. With the promising preliminary reports of the effectiveness of gold compounds in treating

rheumatoid arthritis, however, they appear likely to be utilized more frequently, and therefore an increased number of cases of granulocytopenia due to this cause is to be anticipated.

The most important aspect of treatment of granulocytopenia is preventive. This means careful observation of patients who are receiving therapeutic agents which cause the condition and immediate withdrawal of these agents when the earliest manifestations of the disease appear. There is no specific therapy for the disease, but the observations of Jackson and of Tighe [354] indicate that there is more evidence in favor of pentnucleotide than of any other type of medication. Sufficient data are not yet available for a satisfactory appraisal of the value of yellow bone marrow extract, but preliminary reports indicate that it is clearly worthy of further trial.

The article by Schultz [355] on the present status of granulocytopenia, published in 1939, has an appealing interest, for it was his original publication in 1922 which directed the attention of physicians to the syndrome. After an interval of eighteen years, he again states his views about the disease in general. In his opinion the condition is characterized by a lack of resistance to infection which is attributable to decreased numbers or absence of neutrophils in the circulating blood. This permits the "bacteriologic parasites" of the person afflicted to involve the mucous membranes, the skin and the internal organs. Areas about the anus, the vaginal entrance and the prepuce may be involved. The most frequent finding, however, is an inflammatory diphtheria-like involvement of the throat, palate and lingual tonsil. There is frequently associated ulcerative or necrotic gingivitis. As the lesion of the gums is often the initial visible evidence of the disease, the dentist rather than the physician is often the first to see the patient.

Schultz emphasizes that the practitioner should be on the alert for the clinical characteristics of the disease, the more important of which he lists as follows: the greater incidence in women and in persons who are 40 years of age or more, the combination of gingivitis and tonsillitis and the usual general signs of severe sepsis. He likewise states that jaundice is a sign of the disease, but in our opinion this is not a commonly encountered manifestation of the syndrome in the United States. It is mentioned that the throat may give the appearance of diphtheria

354. Jackson, H., Jr., and Tighe, T. J. G.: Analysis of Treatment and Mortality of Three Hundred and Ninety Cases of Acute Angina, New England J. Med. **220**:729, 1939.

355. Schultz, W.: Der heutige Stand der Agranulozytosefrage, Ztschr. f. ärztl. Fortbild. **35**:647, 1938; Ueber eigenartige Halserkrankungen: (*a*) Monozytenangina; (*b*) Gangräneszierende Prozesse und Defekt des Granulozytensystems, Deutsche med. Wchnschr. **48**:1495, 1922.

but that this disease seldom occurs in persons over 40 years of age and that granulocytopenia is not common in children. It is emphasized that the syndrome of granulocytopenia may mask an underlying blood dyscrasia, such as leukemia or aplastic anemia.

Acknowledgment is made that aminopyrine plays a leading role in causation of the disease. This the author attributes to a constitutional sensitivity to the drug or to development of an anaphylactic state toward it after long usage. Other therapeutic agents, such as arsphenamine, bismuth compounds, gold preparations and, more recently, sulfanilamide, may less frequently be responsible for the production of the syndrome. Mention is made of the usual forms of treatment. Little comment is recorded regarding their efficacy except to say that transfusion with leukemic blood is not of much benefit and that stimulating doses of the roentgen ray are rarely used at present. The author issues an emphatic warning that surgical intervention is contraindicated and if employed may cause a relapse in a patient convalescing from the disease.

An excellent résumé of knowledge concerning granulocytopenia is presented by Reznikoff,[356] in which he reviews data pertaining to the history, etiology, pathologic picture, symptoms and signs, blood picture, prognosis, differential diagnosis and therapy of the syndrome. It is stressed that the condition is a serious one and that in some series of cases there has been a high mortality rate. He believes that the causes of this condition are drugs, fatigue, menstruation and possibly infection. The most common drugs which may play an etiologic role are aminopyrine, dinitrophenol, organic arsenicals, gold salts, sulfanilamide and sulfapyridine. As many persons take these drugs with impunity, it must be assumed that granulocytopenia develops only when a person has an idiosyncrasy toward any one of them. He is in accord with the views of others that the essential lesion in the bone marrow in most cases is an arrest of myeloid maturation. It is his opinion that no specific remedy exists for the disease, although it is proper to administer any remedy which may help and will not harm a patient suffering from this condition. As in previous publications, he emphasizes that monocytosis is a favorable prognostic sign, which is a view shared by other observers.

Rosenthal and Vogel,[357] in the very first sentence of their article, state that granulocytopenia in practically every case can be traced to an underlying sensitivity to certain drugs, such as aminopyridine, arsphenamine, dinitrophenol and, more recently, sulfanilamide. This rather dogmatic statement is probably in a large part correct but is difficult to

356. Reznikoff, P.: Acute Neutropenia (Granulocytopenia), (Agranulocytosis), Internat. Clin. **3**:106, 1939.

357. Rosenthal, N., and Vogel, P.: Agranulocytosis Caused by Sulfapyridine (Sulfanilamide Derivative) in Children, J. A. M. A. **113**:584 (Aug. 12) 1939.

prove. Nevertheless, for purposes of justifiable emphasis, it is a commendable one. They consider that sulfapyridine has a toxicity for the bone marrow equal to or greater than that of sulfanilamide. The chief purpose of their communication is to call attention to the danger of employing sulfapyridine over prolonged or intermittent periods unless frequent study is made of the blood picture. In the few months prior to preparation of their article they had observed 3 cases of granulocytopenia in children, with 2 deaths, following administration of sulfapyridine. They advise that use of the drug be discontinued if the leukocyte count falls to 3,000 or 4,000 per cubic millimeter and not resumed until the number of white blood cells returns to normal. In their opinion, it is dangerous to give the drug over a long period continuously or intermittently in the presence of various types of infection, including pneumonia, in children. According to these observers, the action of sulfapyridine on the bone marrow resembles that of neoarsphenamine to a great extent, as both cause rather definite changes which vary from arrest of maturation to a distinct, almost complete, suppression or hypoplasia of all elements. The observation is again emphasized that monocytosis is a favorable prognostic sign. It is advised that observations on the bone marrow of children who are receiving the drug are important. Caution in its further administration should be used when the cellular content of the sternal marrow falls from a normal value of about 200,000 per cubic millimeter to less than 100,000. Attention is also directed to development of hemolytic anemia following sulfapyridine therapy, which usually manifests itself after a few days of therapy, whereas the development of granulocytopenia follows prolonged or intermittent use of the drug.

In Keefer's [358] opinion, granulocytopenia is the most serious complication of sulfanilamide therapy, as it is associated with such a high mortality rate. The fact is emphasized that in no case has it occurred before the fourteenth to the sixteenth day after the beginning of treatment. While exceptions to this statement will undoubtedly occur, it serves to emphasize the possibility that granulocytopenia is due to a high level of dosage of the drug rather than to the hypersusceptibility of a person to it. Keefer also recognizes that the leukocyte count may fall after use of the drug has been discontinued for several days or when it is resumed after a preliminary withdrawal. In his experience death has generally occurred within two or three days after the onset of granulocytopenia. The importance is stressed of making repeated leukocyte counts in the cases of all persons who have been receiving the drug for a week or longer.

358. Keefer, C. S.: Sulfanilamide: Its Mode of Action and Use in Treatment of Various Infections, New England J. Med. **219**:562, 1938.

Dolgopol and Hobart [359] report 2 cases of granulopenia and a like number of cases of leukopenia in a series of 35 cases of pertussis and pneumonia treated with sulfapyridine. In 1 case of granulopenia complicated by mild aplastic anemia the condition was fatal. The patient was a Negress aged 4 years with pertussis and lobar pneumonia. After 49 Gm. of the drug had been given over a period of sixteen days, the red cell count was 2,770,000 per cubic millimeter, the value for hemoglobin 67 per cent and the leukocyte count 2,000 per cubic millimeter. No polymorphonuclear neutrophil cells were present in the blood films. At necropsy the bone marrow showed a slight decrease in the number of nucleated cellular elements in some areas but was not depleted as a whole. The patient in the second case was a Negro child aged 1 year, with pertussis and bronchopneumonia. At the end of fifteen days, during which time the total dose of the drug was 27 Gm., the red blood cell count was 4,900,000 per cubic millimeter, the value for hemoglobin 60 per cent and the white blood cell count 3,100 per cubic millimeter, with 5 per cent polymorphonuclear neutrophil cells. Recovery followed blood transfusions, pentnucleotide therapy and injections of liver extract. A third patient, a white girl aged 18 months with pertussis and bronchopneumonia, showed a white blood cell count of 4,200 per cubic millimeter, with 24 per cent polymorphonuclear neutrophils, after receiving 13 Gm. of sulfapyridine in six days. An uneventful recovery followed withdrawal of the drug. A fourth patient was a white girl aged 10 months, with pneumonia and pertussis; the leukocyte count was 4,300 per cubic millimeter, with 14 per cent neutrophils, after an intake of 3 Gm. of sulfapyridine in four days. As the concentration of the drug in the blood was only a trace, the therapy was not discontinued. Eight days later there was an increase in the number of white blood cells and neutrophils, and the patient recovered without complications.

That sulfapyridine may occasionally depress the bone marrow is not surprising, according to these authors. This is because the drug contains the benzamine group, which some consider to be responsible for the injurious action of a number of drugs on myeloid tissue. The leukopenia is attributed to an arrest in maturation of the leukopoietic elements, but at the same time the erythropoietic elements may be affected, as is indicated by reduction of the number of nucleated red blood cells in bone marrow smears.

Several pertinent questions are raised by these investigators relating to the action of sulfapyridine in producing changes in the peripheral

359. Dolgopol, V. B., and Hobart, H. M.: Granulocytopenia (and Leukopenia) in Sulfapyridine (Sulfanilamide Derivative) Therapy, J. A. M. A. **113**:1012 (Sept. 9) 1939.

blood. They call attention to the fact that a relatively large total dose has usually been given to patients who show evidence of injury to the bone marrow. This evidence does not necessarily indicate that a high concentration in the blood results in deleterious effects. They are in accord with the view, which has hitherto been emphasized in relation to aminopyrine, that an individual sensitivity to sulfapyridine probably plays a role in the production of neutropenia in some cases. The possibility that a preliminary course of the drug may sensitize a person to subsequent doses must be considered, although the evidence favoring this mechanism of the production of toxic manifestations is not wholly convincing. They recognize that certain infections, such as those due to streptococci and typhoid fever, cause granulocytopenia independently of sulfapyridine therapy, but they conclude that pertussis can probably be excluded from the group of diseases producing such an effect. A warning is sounded against using excessively large amounts of sulfapyridine, and the recommendation of Whitby and others [360] to keep the blood level at 8 mg. per hundred cubic centimeters and to use 23 Gm. of the drug per week for an adult is again emphasized. It is suggested that blood counts should be made twice weekly when sulfapyridine is being given and that they should be continued for two weeks after withdrawal of the drug. Such a recommendation is rational, but in our opinion it is one which is unlikely to be followed as frequently as is desired.

The case of a woman aged 22 who had fatal granulocytopenia following the taking of 35 Gm. of sulfanilamide over a period of fifteen days is reported by Corr and Root.[361] The patient had been ill with a severe infection of the throat for two weeks, and at the end of that time the white blood cell count was 800 per cubic millimeter, with 8 per cent neutrophils. Although slight improvement followed the use of pentnucleotide and a blood transfusion, death occurred on the fifteenth day of the illness. They authors emphasize that 9 cases of fatal granulocytopenia apparently caused by sulfanilamide were reported prior to October 1938, together with a few in which recovery took place. It is their opinion, in which we concur, that an unknown number of deaths have probably occurred, some of which have been unrecognized and others of which have not been reported. Likewise, their surmise that many more cases are to be expected with the increasing use of this valuable drug is probably correct. Since it is recognized that such a serious com-

360. Whitby, L. E. H., and others, in Discussion on Use of Sulphanilamide and Allied Drugs in Treatment of Human and Animal Diseases, Proc. Roy. Soc. Med. **32**:349, 1939. Whitby, L. E. H.: Chemotherapy of Bacterial Infections (Bradshaw Lecture), Lancet **2**:1095, 1938.

361. Corr, P., and Root, R. N.: Death from Granulocytopenia After Sulfanilamide Therapy, J. A. M. A. **112**:1939 (May 13) 1939.

plication can result from the use of this drug, it becomes necessary to adopt some simple yet effective means of averting it. The suggestion that patients receiving sulfanilamide should have repeated examinations of the blood is not practical, for strict enforcement would curtail use of the drug and thereby cost more lives than could be saved by the prevention of deaths from agranulocytic angina. Even frequent examinations of the blood would not forestall all deaths from granulocytopenia, for the condition may not appear until several days after use of the causative agent has been discontinued. Two suggestions are made which are worthy of serious consideration, as follows: 1. Any patient with toxic symptoms should be denied further use of the drug or should be observed very carefully. 2. As granulocytopenia in all cases has developed after administration of 25 to 35 Gm. of sulfanilamide or more, the practitioner can safely give up to 20 Gm. of the drug before being concerned about granulocytopenia. In general we are in accord with this statement, for at present our knowledge seems to indicate that this serious complication follows ingestion of substantial amounts of the substance. The possibility, however, that it may result from a relatively small quantity when consumed by a person who has a specific sensitivity to it cannot be completely dismissed.

A case of granulocytopenia associated with a white blood cell count of 1,200 per cubic millimeter and no neutrophils in the circulating blood, developing in a patient with acute tonsillitis and pharyngitis in which the predominating organism was streptococci in short chains, is reported by Shullenberger.[362] The condition became apparent after 52.3 Gm. of sulfapyridine had been administered over a period of twenty-one days. Recovery followed withdrawal of sulfapyridine and administration of pentnucleotide. The author considers that it is impossible at present to state that sulfapyridine is less active than sulfanilamide in causing granulocytopenia. It is our estimate, wholly unsupported by facts, that when given in adequate doses one is as likely to cause granulocytopenia as the other.

Coxon and Forbes [363] report the occurrence of granulocytopenia in a patient with typhoid fever. The condition developed after a total dose of 54 Gm. of sulfapyridine in seventeen days. The authors state that while leukopenia is common with typhoid fever, granulocytopenia is rare in this association. We can confirm this statement, having

362. Shullenberger, W. A.: Agranulocytosis Following Treatment of Bacterial Infections with Sulfapyridine: Case Report with Review of Literature, J. Indiana M. A. **32**:415, 1939.

363. Coxon, R. V., and Forbes, J. R.: Agranulocytic Angina Following Administration of M. and B. 693 (Sulfapyridine, Sulfanilamide Derivative), Lancet **2**:1412, 1938.

observed such a case, in which the leukocyte count was 300 per cubic millimeter. It is the conclusion of the authors that in their case the granulocytopenia was due mainly to the sulfapyridine, although the typhoid fever may have been a contributing factor. They believe that sulfapyridine is probably less toxic than sulfanilamide but that in certain cases the former drug may cause injury to the leukopoietic system.

Myhre [364] records a case of granulocytopenia associated with the therapeutic use of sulfanilamide and gives a bibliography including 25 other such cases. The patient, a woman, aged 53, with hypertension and an infection of the urinary tract due to B. coli, received 18.9 Gm. of sulfanilamide in twenty-two days. The lowest white blood cell count was 2,200 per cubic millimeter, with 8 per cent myelocytes and 3 per cent "staffs." Granulocytes with "segmented and staff" nuclei disappeared completely from the sternal bone marrow. A feature of this case was the appearance of large numbers of stipple cells in the circulating blood. This phenomenon most frequently occurs in cases of lead poisoning, but it may be present with many anemias, especially those due to increased destruction of blood. This may account for the appearance of stipple cells in this patient, although Myhre has found no previous mention in the literature of stippling after sulfanilamide medication. Of the 26 cases reported in the literature, 15 terminated fatally. The drug should be used with caution and never for more than seven to ten days at a time. Should a second course be required, the blood should be examined frequently, especially if there is a rise in body temperature. The treatment of granulocytopenia, according to Myhre, should begin with intramuscular administration of liver extract, and if this is unsuccessful nucleic acid preparations and blood transfusions should be given a trial.

A case of fatal granulocytopenia, with necropsy observations and a review of the literature dealing with this subject, is reported by Shecket and Price.[365] The patient, a 45 year old man, had a pulmonary infarction ten days after an operation for left indirect inguinal hernia. Sixty-four grams of sulfanilamide was administered in fifteen days. Cyanosis and dyspnea were noted in eight days, nausea and vomiting appeared in ten days and an erythematous macular rash developed thirteen days after initiation of therapy. Neutropenia was first observed on the sixteenth day, which was twenty-four hours after cessation of sulfanilamide therapy. Death occurred seven days after withdrawal of

364. Myhre, H.: Sulphanilamide Agranulocytosis, Acta med. Scandinav. **99**: 614, 1939.

365. Shecket, H. A., and Price, A. E.: Fatal Granulocytopenia Following Administration of Sulfanilamide, J. A. M. A. **112**:823 (March 4) 1939.

the drug. No other therapeutic preparations which are known to cause granulocytopenia were given. Necropsy showed, among other observations, a myeloblastic arrest of the cells of the bone marrow. These authors are not in accord with the belief of others that the action of sulfanilamide on the bone marrow is the result of a specific idiosyncrasy but are of the opinion that the quantity and prolonged use of the drug are the significant factors. In support of this, they make the statement that the total dose of sulfanilamide in their own cases and the 9 similar cases then reported in the literature ranged from 35 to 64 Gm., with an average of 50 Gm. These amounts were given over periods of from fifteen to thirty days, with an average of twenty-seven days. The authors give the following pertinent advice, which may well be heeded by those who use the drug indiscriminately: "The efficacy of sulfanilamide in a given condition should be demonstrated after 4 to 7 days. If no improvement is noted within that period, the continued use of the drug is of doubtful value." Significant warning signals are cutaneous eruptions, hyperpyrexia, jaundice, reduction in the red blood cell count and either an abrupt rise or an abrupt fall in the number of white blood cells. Although appearance of any one of these signs is not necessarily indicative of the toxic action of sulfanilamide, thoughtful consideration should be given to their appearance in a patient who is receiving the drug. Emphasis is given to the growing opinion that granulocytopenia may be a late development in the course of sulfanilamide therapy, as is indicated by the fact that in 6 of the 10 cases reported in the literature the condition did not develop until from one to four days after the medication had been discontinued.

Hall [366] emphasizes that sulfanilamide may be responsible for two important abnormalities of the circulating blood: It may cause an acute hemolytic anemia, which is the most common untoward effect but from which recovery usually occurs, or it may produce granulocytopenia, which has a sinister outlook. According to this observer, of the 12 cases which had been reported in the literature up to that time, 8 terminated fatally. Sulfanilamide possesses the benzene ring with the attached amino group, and in this respect it resembles aminopyrine, which is known to cause granulocytopenia in some persons. The author reports the case of a boy aged 9 years who was treated for pneumonia with 45 Gm. of the drug over a period of three weeks. At the end of this time the white blood cell count was 1,900 per cubic millimeter, of which 12 per cent were neutrophils. Later the count decreased to 850 cells per cubic millimeter, and no neutrophils could be found on exam-

366. Hall, B. E.: Influence of Sulfanilamide on Blood, Proc. Staff Meet., Mayo Clin. **14**:155, 1939.

ination of the blood films. Death occurred despite treatment with pentnucleotide and liver extract given intramuscularly and yellow bone marrow extract (Stearns) given by mouth. When granulocytopenia is observed, it is recommended that use of the drug be stopped immediately, that fluids be forced by mouth and injected intravenously and that yellow bone marrow extract be given in daily doses of 50 to 200 capsules (each capsule containing 0.22 Gm.). The results in his experience have been disappointing after use of pentnucleotide, liver extract and blood transfusions. A warning is given regarding the effect of sulfanilamide in the breast milk of mothers on nursing infants. Although the amount in breast milk is small and is unlikely to be harmful, it is known that the bone marrow of infants and young children is especially susceptible to toxins and chemical agents. Care should be taken, therefore, to observe the infant for toxic reactions.

According to Cutler and Crane,[367] 9 cases of granulocytopenia following sulfanilamide therapy, with 2 recoveries, had been reported at the time their article was written. They include a personal communication from P. H. Long, who reports that 6 cases have occurred at the Johns Hopkins Hospital, with 2 recoveries. It is concluded that "undoubtedly" there is a greater incidence of this complication following sulfanilamide therapy than has been reported. The case of a young woman with acute bilateral pyogenic salpingitis who had granulocytopenia following administration of sulfanilamide is reported. After twenty-one days of therapy the white blood cell count fell to 2,600 per cubic millimeter, with 1 per cent polymorphonuclear cells. There was a coincident fall in the red blood cell count to 2,400,000 per cubic millimeter. The body temperature rose sharply, and the patient complained of sore throat, although there was only a slight infection of the fauces. Transient jaundice, persisting for over two days, was noted on the fourteenth day of treatment. Recovery followed multiple blood transfusions, pentnucleotide therapy and withdrawal of sulfanilamide. The authors recommend that patients receiving the drug should have daily erythrocyte and leukocyte counts. The possibility that the granulocytopenia may have been due to administration of other substances, such as aminopyrine, cannot be dismissed from a review of this article, as there is no statement concerning the administration of other drugs to the patient. Such a possibility is unlikely, however, as it is not common to observe hemolytic anemia associated with granulocytopenia due to aminopyrine. The authors emphasize that the course of events in this case is in accord with Keefer's[358] statement that granulocytopenia

367. Cutler, I. L., and Crane, E. J.: Agranulocytosis Caused by Sulfanilamide: Recovered Case, New England J. Med. **221**:231, 1939.

following sulfanilamide therapy has never been known to occur before the fourteenth day.

Pearson [368] reports the case of a 60 year old woman who had the syndrome of granulocytopenia with a white blood cell count of 600 per cubic millimeter and a neutrophil percentage of 2. The condition was recognized after a total dose of 34.5 Gm. of sulfanilamide had been taken over a period of twenty-three days. A latent period of six days elapsed between omission of the drug and the appearance of warning symptoms. The author makes the suggestion that perhaps the duration of the treatment is of greater importance in relation to the development of granulocytopenia than is the total dose of the drug. The treatment in this case, which was unique but did not prevent a fatal outcome, consisted of a transfusion of 300 cc. of citrated blood from a donor suffering with myeloid leukemia associated with a total white blood cell count of 120,000 per cubic millimeter.

Taub and Lefkowitz [369] emphasize that sulfanilamide is a potential marrow poison the effect of which is cumulative. According to them, there is a causal relation between the size of the dose and granulocytopenia. They state that the fatal cases of granulocytopenia due to sulfanilamide followed a total dose varying from 38 to 94.5 Gm. given in periods of from eighteen to forty days. Their own patient, who died, received 44 Gm. in twenty-one days. Evidence of granulocytopenia was not discovered until three days after the medication was discontinued.

A patient with subacute bacterial endocarditis who was treated with sulfanilamide and succumbed with the symptoms of granulocytopenia is reported by Sailer.[370] A total dose of 282.6 Gm. of the drug was given in twenty-three days. Examination of the bone marrow at necropsy showed alternating areas of aplasia and myeloid and lymphoid hyperplasia, with the former lesion predominating. Focal areas of necrosis were present in the intermediate zone of the liver. The author believes that these pathologic lesions were associated with sulfanilamide therapy and were not due to the original disease process.

According to the report of Gayus, Green-Armytage and Baker,[371] a woman aged 24 had granulocytopenia after receiving 39.5 Gm. of

368. Pearson, H. E. S.: Fatal Agranulocytosis After Sulfanilamide Therapy, Brit. M. J. **1**:1031, 1939.

369. Taub, J., and Lefkowitz, L.: Agranulocytic Angina Due to Sulfanilamide (Case), New York State J. Med. **39**:1659, 1939.

370. Sailer, S.: Subacute Bacterial Endocarditis Treated with Sulfanilamide Resulting in Granulocytopenia and Death, Am. J. Clin. Path. **9**:269, 1939.

371. Gayus, I. K.; Green-Armytage, V. B., and Baker, J. K.: Puerperal Agranulocytosis Following Sulfanilamide Treatment: Record of Fatal Case, Brit. M. J. **2**:560, 1939.

sulfanilamide in seventeen days, after a streptococcic infection following a normal delivery. The white blood cell count decreased to 850 per cubic millimeter, and no neutrophils were seen in a count of 150 cells. Death ensued despite use of 100 cc. of pentnucleotide and administration of 1,100 cc. of citrated blood by the continuous drip method. The authors warn that a complete examination of the blood should be made, even in the absence of symptoms of granulocytopenia, after 25 Gm. of sulfanilamide has been given.

McNab and Parry [372] report the case of a woman aged 30 with puerperal fever. The white blood cell count was 1,400 per cubic millimeter with 8 per cent neutrophils after the patient had received 76 Gm. of sulfanilamide in fourteen days. The red blood cell count fell to 2,590,000 per cubic millimeter, with a value for hemoglobin of 45 per cent. Recovery followed the use of 170 cc. of pentnucleotide intramuscularly in doses of 10 cc., a blood transfusion and use of a liver extract (Campolon) and of ferrous sulfate.

A summary is given by Butt, Hoffman and Soll [373] of the literature dealing with experimental production of granulocytopenia with aminopyrine in man and in animals. It is their opinion that the drug has a toxic action on the bone marrow in a majority of animals, but in only a small proportion are evidences of this reflected in the peripheral blood. In their experiments, 2 dogs which received 250.9 Gm. and 255.5 Gm. of aminopyrine respectively over periods of ten and one-half and nine months showed marked aplasia of the bone marrow. The authors consider that the action of the drug in the given doses is not unlike that of benzene and is somewhat selective, as destruction of myeloid elements precedes aplasia of the erythroblastic cells. The other dogs which were studied died of systemic toxic effects of aminopyrine before changes in the bone marrow were sufficiently marked to be unequivocal. The authors conclude that aminopyrine, in addition to its direct systemic toxic effect, has a selective action on the bone marrow. It is important to note that in the case of 1 of the 2 animals with severe aplasia of the bone marrow the leukocyte count was as low as 350 per cubic millimeter. It is the opinion of the authors that the toxic action of aminopyrine is far more frequent than Rawls's [374] figures would indicate. Rawls expressed the opinion, estimated on clinical observations, that 1 to 2

372. McNab, D. J. N., and Parry, D. E.: Agranulocytosis After Sulfanilamide: Recovery, Brit. M. J. **2**:565, 1939.

373. Butt, E. M.; Hoffman, A. M., and Soll, S. N.: Experimental Production of Neutropenia with Aminopyrine, Arch. Int. Med. **64**:26 (July) 1939.

374. Rawls, W. B.: The Effect of Amidopyrine on Red, White and Polymorphonuclear Blood Cells of a Series of One Hundred Patients, Am. J. M. Sc. **192**:175, 1936.

per cent of patients show susceptibility to the drug, as indicated by changes in the peripheral blood.

Dardinski and Lyddane [375] report the case of a man aged 65 who had fatal granulocytopenia after taken causalin (aminodimethylpyrazolonquinoline sulfonate) for relief of arthritis. The patient, who died on the same day on which he was admitted to the hospital, had been ill for a week with fever and with symptoms referable to the throat. The leukocyte count was 560 per cubic millimeter, with 29 per cent neutrophils, just before death.

Coventry [376] records an interesting case of nonfatal granulocytopenia attributed to the therapeutic use of cinchophen in doses of 7½ grains (0.48 Gm.) every three hours for three weeks. This medicament, which was taken in combination with anacin (acetylsalicylic acid, acetophenetidin, quinine sulfate and caffeine), resulted in improvement in the rheumatic fever from which the patient was suffering. It is our opinion that the patient undoubtedly had granulocytopenia, for the leukocyte count decreased to 2,650 per cubic millimeter, and neutrophils were completely absent from the blood films. To prove that the granulocytopenia was due to cinchophen is another matter, difficult to demonstrate conclusively. It might have been, as the author suggests, that one of the other drugs which the patient was receiving caused the condition. Then, again, it must be considered that aminopyrine in some form, disguised by a trade name, may have been taken by the patient without the physician's knowledge. The possibility that cinchophen may have been the offending drug cannot be denied; on the other hand, the facts do not offer conclusive proof that this was the case.

Ives [377] reports the case of a man aged 52 with fulminant necrosing pharyngitis accompanied with complete granulocytopenia who recovered after the use of prontosil (now known as azosulfamide; disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino - 1′-hydroxynaphthalene - 3′,6′disulfonate) and sulfanilamide. He considers that the angina and granulocytopenia were due to a hemolytic streptococcic infection and that the therapeutic preparations exerted a definite and specific action against the organism. Although recovery is attributed chiefly to this therapy, it is conceded that pentnucleotide and liver extract therapy were also of some benefit. Although this patient recovered, it is our opinion that the administration of sulfanilamide and similar drugs to a

375. Dardinski, V. J., and Lyddane, E. S.: Agranulocytic Angina: Report of a Case Due to Causalin, J. A. M. A. **112**:134 (Jan. 14) 1939.

376. Coventry, W. D.: Granulocytopenia, Minnesota Med. **22**:117, 1939.

377. Ives, R. F.: Hemolytic Streptococcic Angina with Agranulocytosis Treated with Prontosil and Sulphanilamide, Ann. Int. Med. **12**:882, 1938.

patient with any prior damage to the bone marrow should be done with extreme caution; certainly excessive doses should be avoided.

Granulocytopenia with a white blood cell count of 4,200 per cubic millimeter and 33 per cent neutrophils developed on the third day in a man aged 40 after an operation for a perforated appendix, as reported by Richmond.[378] Recovery followed intravenous injection of adenine sulfate in 2 Gm. doses. The author regards this substance as a nontoxic drug which is specific in stimulating myeloblastic activity in patients with granulocytopenia. It is likely that this patient had severe sepsis with a poor response of the white blood cell-forming elements, as indicated by the total leukocyte count. No positive statement is made, however, that sulfanilamide or sulfapyridine was not given.

Jackson and Tighe[354] present a comprehensive appraisal of the different forms of treatment administered in 390 cases of acute agranulocytic angina, based on a survey of the literature which has appeared since 1933. Although attempts to draw conclusions by this method may have its defects, they consider it the best available method of evaluating the various therapeutic agents so far advocated for this disease.

The syndrome is delineated as an acute disease characterized by extreme leukopenia and granulopenia; the red blood cells and platelets are essentially unaltered; hemorrhagic manifestations are rare; an occasional immature white blood cell may appear in the blood at the height of the disease; there is no enlargement of the liver and spleen, and no lymphadenopathy is present other than that which is due to local sepsis. Death may terminate the illness within thirty-six hours of the onset, and recovery, if it takes place, usually occurs within two weeks. It is generally agreed, according to the authors, that many cases are caused by aminopyrine, dinitrophenol and "similar compounds"; they consider that the characteristic lesion in the bone marrow is arrest of maturation of the granular white cell series at the myeloblast stage. It is properly emphasized that the disease must be differentiated from aleukemic leukemia, aplastic anemia, leukopenia due to overwhelming sepsis and chronic leukopenia due to divers causes. In an effort to evaluate accurately the effects of treatment, all patients who received inadequate treatment, as well as those who recovered when similar therapy was given, were eliminated. The death rate in these two groups of patients was 73 per cent, which is the same as that observed with patients who received no specific therapy whatever.

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378. Richmond, E. L.: Granulocytopenia Following Surgical Sepsis and Treated with Adenine Sulfate, New England J. Med. **221**:267, 1939.

These authors, after a survey of the literature, present the following conclusions concerning the effectiveness of various forms of therapy in the disease:

	Mortality, Per Cent
1. No specific therapy	70-80
2. Transfusions	74
3. Stimulating doses of roentgen ray	67
4. Parenteral liver extract	62
5. Pentnucleotide	35
6. Adenine sulfate	20
7. "Leukocytic cream"	17
8. Yellow bone marrow extract	10

The authors conclude that neither roentgen therapy nor blood transfusion alters the mortality. Likewise, from these figures liver extract seems to be ineffective. Treatment with yellow bone marrow extract, leukocytic cream and adenine sulfate is associated with a low death rate and accordingly deserves a further trial. On account of the small number of patients who have received these forms of therapy, however, it is not possible to appraise their ultimate value at present. As the mortality in 85 cases treated with pentnucleotide was 35 per cent, they conclude that use of this drug in doses of 40 cc. daily "is the most promising form of specific therapy in this disease."

To us, from a consideration of the literature and from personal experience, it would appear that the most effective management of patients with agranulocytic angina is as follows:

1. Simultaneous administration of pentnucleotide intramuscularly in doses of 40 cc. daily and of yellow bone marrow extract orally in daily doses of 300 to 500 Gm.

2. Treatment of the lesions of the mouth and throat with bland saline irrigations and avoidance of surgical intervention in these areas during the acute process.

3. Prohibition of all drugs, such as aminopyrine, sulfanilamide and allied substances, which are known to cause granulocytopenia.

4. Use of blood transfusions for the occasional patient who has had anemia prior to development of granulocytopenia or who shows anemia during the course of the disease.

HODGKIN'S DISEASE, LYMPHOSARCOMA AND LYMPHOMATOID DISEASES

Ewing[379] classifies tumors of the lymph nodes as lymphadenoma (multiple giant follicular lymphadenoma; Brill's disease; gastrointestinal

379. Ewing, J.: General Pathology of Lymphosarcoma, Bull. New York Acad. Med. **15**:92, 1939.

pseudoleukemia); lymphocytoma (systemic pseudoleukemia; lymphocytic leukemia; malignant disseminating lymphocytoma; plasmacytoma; solitary lymphoma), and reticulum cell lymphosarcoma (large round cell lymphosarcoma affecting many regions and organs). Gastrointestinal pseudoleukemia is a peculiar systemic disease producing myriads of small lymphomas in the mucosa from the mouth to the anus, without ulceration, and extending to many chains of lymph nodes and the spleen. The course is steadily progressive and active, with fever, anemia, diarrhea, emaciation, peritonitis and death within a few months or years. Structurally, the growth shows well formed lymph follicles without the diffuse growth of malignant tumors. The cause is unknown.

An excellent critical review of the present status of Hodgkin's disease is presented by Krumbhaar.[380] It is too complete to review here, and the article should be studied by any one working with Hodgkin's disease. In a general review of reticulum cell sarcoma and giant follicle lymphoma (grouped as malignant lymphoma), Jackson [381] points out that besides the lymph nodes, the spleen, liver, pancreas, gastrointestinal tract, bones, skin, lung, heart, nasopharynx, breast, ovary and testicle may be involved (in descending order). Involvement of the central nervous system is not rare. Surgical intervention may be of value in selected cases of Hodgkin's disease when the process is limited to accessible glands. Roentgen therapy gives the best responses, but the danger of primary swelling of the glands producing pressure symptoms and of toxemia from destruction of large amounts of tissue must be kept in mind. Hodgkin's disease is divided into Hodgkin's lymphoma, Hodgkin's granuloma and Hodgkin's sarcoma, with prognosis decreasing in hopefulness in the order named.

Epstein [382] comments on the fact that Hodgkin's disease is less frequent and less malignant in women than in men. Glandular activity may possibly exert a restraining influence on the condition.

In cases of lymphogranulomatosis and of Banti's disease, Schousboe [345] interprets the anemia, leukopenia, thrombopenia, hyperplasia of the bone marrow and immaturity of the leukocytes as evidences of splenic inhibition, remediable by splenectomy.

Baker and Mann [383] report a summary of the clinical findings in 65 cases of Hodgkin's disease.

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380. Krumbhaar, E. B.: The Present Status of Hodgkin's Disease, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 148.

381. Jackson, H.: Hodgkin's Disease and Allied Disorders, New England J. Med. **220**:26, 1939.

382. Epstein, E.: Sex as a Factor in the Prognosis of Hodgkin's Disease, Am. J. Cancer **35**:230, 1939.

383. Baker, C., and Mann, W. N.: Hodgkin's Disease: A Study of Sixty-Five Cases, Guy's Hosp. Rep. **89**:83, 1939.

A contribution of some significance is that of Parsons and Poston [384] concerning the similarity of the histologic structure of glands in cases of Hodgkin's disease and in cases of chronic brucellosis. Brucella organisms were cultured from lymph nodes in which the histologic picture was identical with that of Hodgkin's disease. The glands of a patient with chronic brucellosis may show complete destruction of the original architecture of the lymph node, pronounced eosinophilia, focal scarring, production of large pale mononuclear cells and production of Dorothy Reed cells. Lesions of chronic brucellosis may be associated with negative agglutination reactions, negative brucellergin reactions and negative or low phagocytic indexes, but the cultures yield the organisms.

Rabson's [385] description of the granulomas associated with brucellosis in man is perfectly compatible with Parson and Poston's observations, and the relation of brucellosis and Hodgkin's disease is a subject for further study.

Uhlenhuth and Wurm,[386] although unable to transmit Hodgkin's disease to animals, regard it as an infection. They do not consider tuberculosis, streptothrix, diphtheroid bacilli or the elementary bodies of Gordon and Gow as etiologic factors. They confirm the work of others, who have shown that a constituent of the eosinophils is the cause of a positive result in Gordon's test.

Pittaluga [387] concludes that differences between megakaryoblasts, megakaryocytes and cells of Sternberg make it unlikely that Hodgkin's disease represents a systemic metaplasia of megakaryocytes.

Scott and Robb-Smith [388] describe a new syndrome which they call histiocytic medullary reticulosis. This condition, formerly grouped with Hodgkin's disease, is characterized by fever, wasting and generalized lymphadenopathy associated with splenomegaly, hepatomegaly and, in the final stages, jaundice, purpura, anemia and profound leukopenia. On postmortem examination a systematized hyperplasia of histiocytes actively engaged in the phagocytosis of erythrocytes is observed. The

384. Parsons, P. B., and Poston, M. A.: The Pathology of Human Brucellosis: Report of Four Cases with One Autopsy, South. M. J. **32**:7, 1939.

385. Rabson, S. M.: Pathologic Anatomy of Human Brucellosis, Am. J. Clin. Path. **9**:604, 1939.

386. Uhlenhuth, P., and Wurm, K.: Untersuchungen zum Problem der Hodgkinschen Krankheit: I. Experimentelle Untersuchungen zur Ätiologie der Hodgkinschen Krankheit, Ztschr. f. d. ges. exper. Med. **105**:205, 1939.

387. Pittaluga, G.: Cellules de Sternberg et mégacaryocytes, Sang **13**:833, 1939.

388. Scott, R. B., and Robb-Smith, T.: Histiocytic Medullary Reticulosis, Lancet **2**:194, 1939.

authors describe 4 cases and summarize the details of 6 cases reported by others. The course is rapid, with death in from six to thirty-two weeks (average, fifteen weeks).

Velasco Montes [389] notes that the bone marrow is involved in only about one half of the patients with Hodgkin's disease and therefore that gland puncture has an advantage over sternal puncture as a diagnostic procedure. Classification of "adenograms" is based on the predominance of certain cell types. Glandular puncture is less annoying to the patient than exploratory excision (removal of a biopsy specimen); there is less danger of a flare-up of the disease process, and the procedure may be repeated as often as desired. Interpretation of the cellular material is often difficult, however, especially after roentgen therapy. When there is much sclerosis or when glands are not accessible, splenic puncture may be of diagnostic value.

Changes similar to those resulting from injection of extracts of lymph nodes from patients with Hodgkin's disease or from leukocytic cream of human blood follow injection of monkey bone marrow extract intracerebrally into rabbits. Encephalopathy develops, with ultimate necrosis (King [390]).

Plá, Pérez Sánchez and Granotich [391] consider that a virus is present in cases of malignant lymphogranuloma which may cause neurologic symptoms. Lymph nodes or metastatic nodules may give rise to symptoms by compression of the lateral columns of the spinal cord, the brain or the nerve roots.

Liebegott [392] obtained a positive result from a Gordon test of lymphogranulomatous tissues only when a considerable number of eosinophils were present.

The occurrence of eosinophilic hyperleukocytosis in association with Hodgkin's disease is reported by Major and Leger.[393] The leukocyte count reached a maximum of 169,000 per cubic millimeter, with 95 per cent eosinophils. The absence of myelocytes and splenomegaly and the

389. Velasco Montes, F.: Ueber die hämatologische Diagnose der Lymphogranulomatose (Hodgkinsche Krankheit), München. med. Wchnschr. **86**:255, 1939.

390. King, L. S.: Encephalopathy Following Injections of Bone Marrow Extract, J. Exper. Med. **70**:303, 1939.

391. Plá, J. C.; Pérez Sánchez, A., and Granotich, J. P.: Neurolymphogranulomatous Syndromes, Arch. urug. de med., cir. y especialid. **14**:513, 1939.

392. Liebegott, G.: Histologisches Bild und Gordon-Test bei der Lymphogranulomatose, Verhandl. d. deutsch. path. Gesellsch. (1938) **31**:459, 1939; Untersuchungen zum Problem der Hodgkinschen Krankheit: II. Ueber die Beziehungen zwischen histologischem Bild und Gordon-Test bei Lymphogranulomatose, Ztschr. f. d. ges. exper. Med. **105**:241, 1939.

393. Major, R. H., and Leger, L. H.: Marked Eosinophilia in Hodgkin's Disease, J. A. M. A. **112**:2601 (June 24) 1939.

positive evidence of Hodgkin's disease from biopsy of material from a lymph node differentiated this condition from leukemia.

In Dunn's [394] case of lymphosarcoma removal of the affected inguinal nodes and high voltage roentgen therapy were followed by no evidence of recurrence for over three years.

Of sarcomatous growths of the stomach observed at the Mayo Clinic, Madding [395] found 30 per cent to be lymphosarcoma, 32 per cent round cell sarcoma, 8 per cent malignant lymphocytoma and 11 per cent Hodgkin's disease. Metastatic lesions (65 to 70 per cent) occurred most frequently in the regional (gastric) lymph nodes. The average age of the patients was 46 years, with a preponderance of men (6:1). Pain was the most common symptom, being generalized either in the abdomen or in the epigastrium. Free hydrochloric acid was absent in the gastric contents of 67 per cent of the patients, and blood was not found as frequently as in cases of carcinoma. The lesion is very radiosensitive, but operation is advocated whenever possible.

In describing 5 cases of lymphosarcoma of the stomach, Taylor [396] comments on the difficulty of making a clinical diagnosis, as there are no distinctive symptoms and no characteristic roentgen picture. Complete surgical removal of the lesion is desirable but not always feasible. Roentgen therapy has produced complete clinical remissions lasting up to eight years. Of 147 patients with primary lymphosarcoma of the stomach mentioned previously in the literature, 13 are living and well five to twenty-two years after discovery of the lesion. (A bibliography of articles describing these cases, from 1893 to 1937, is appended.) Cases of lymphosarcoma of the stomach are reported in Cabot cases 24501 and 25011,[397] and a primary isolated case of Hodgkin's disease of the stomach is described by Avent.[398] In Martin, Denise and Muller's case [399] lymphosarcoma of the small intestine occurred in a 6 year old child.

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394. Dunn, G. R.: Lymphosarcoma of Inguinal Glands: Case Report, Minnesota Med. **22**:284, 1939.

395. Madding, G. F.: Lymphosarcoma of the Stomach with Particular Reference to the Reticulum Cell Variety, Proc. Staff Meet., Mayo Clin. **14**:202, 1939.

396. Taylor, E. S.: Primary Lymphosarcoma of Stomach, Ann. Surg. **110**: 200, 1939.

397. Lymphosarcoma of Stomach, Cabot Case 24501, New England J. Med. **219**:961, 1938. Hodgkin's Sarcoma of Stomach, Duodenum and Jejunum, Cabot Case 25011, ibid. **220**:31, 1939.

398. Avent, C. H.: Primary Isolated Lymphogranulomatosis (Hodgkin's Disease) of Stomach: Report of a Case, Arch. Surg. **39**:423 (Sept.) 1939.

399. Martin, J. F.; Denise, H., and Muller, B.: Un cas de sarcome lymphoblastique de l'intestin grêle chez un enfant de six ans, Lyon méd. **162**:393, 1938.

Bernard [400] comments on the periodicity of the fever associated with Hodgkin's disease, comparing it with that observed with undulant fever and tuberculosis. In Townsend and Braunstein's [401] case of Hodgkin's disease there was severe macrocytic anemia (mean corpuscular volume, 146 cubic microns). The secretion of hydrochloric acid was not abnormal. There was a reticulocyte response to liver extract. At autopsy, gross infiltration of the bone marrow with Hodgkin's tissue was noted. There was no bilirubinemia, and no neurologic changes were observed. Possible causes were a prolonged dietary deficiency or involvement of the liver.

Behrend's [402] patient had a Hodgkin's tumor of the anterior portion of the mediastinum and chest wall. Roentgen therapy caused diminution in size of the mass, and the tumor was removed surgically. No recurrence was noted in eighteen months. In Harrell's case [403] there was invasion of the pericardium and of the gallbladder. Eight cases in which there were pericardial lesions had been reported previously. Hardin's [404] patient had a massive collapse and cavitation of the lungs. In Pfahler's [405] case of mediastinal glandular tuberculosis in an adult there were some features requiring differentiation of the condition from Hodgkin's disease. The patient recovered. In Kravitz' [406] case the disease involved the eyelid.

A case of aleukemic lymphosarcoma cell leukemia in a 64 year old man is described by Varadi.[407] Data obtained by sternal and lymph gland aspiration showed lymphoblastomatous proliferation, with 21 to 66 per cent of the cells in the peripheral blood of lymphoid origin and a total leukocyte count ranging from 5,500 to 15,500 per cubic millimeter.

Giordano's [408] series of patients with Hodgkin's disease included 65 men and 37 women ranging from 11 to 80 years of age (the majority

400. Bernard, A.: La fièvre ondulante dans la maladie de Hodgkin, Bruxelles-méd. **19**:288, 1939.

401. Townsend, S. R., and Braunstein, A. L.: Hyperchromic Macrocytic Anemia in Association with Hodgkin's Disease, Canad. M. A. J. **41**:254, 1939.

402. Behrend, M.: Hodgkin's Disease of Anterior Mediastinum and Anterior Chest Wall, Am. J. Surg. **45**:348, 1939.

403. Harrell, G. T.: Hodgkin's Disease with Invasion of Pericardium and Gall Bladder: Review of Literature and Report of Case with Autopsy, Arch. Path. **28**:58 (July) 1939.

404. Hardin, B. L.: Case of Hodgkin's Disease with Massive Collapse and Cavitation of Lung, Am. J. M. Sc. **197**:92, 1939.

405. Pfahler, G. E.: Mediastinal Glandular Tuberculosis in Adult Resembling Hodgkin's Disease: Recovery of Case, Am. J. Roentgenol. **41**:742, 1939.

406. Kravitz, D.: Hodgkin's Disease of the Lid: Report of Case, Arch. Ophth. **21**: 844 (May) 1939.

407. Varadi, S.: Réticulosarcome leucémique (réticulo-lympholeucosarcomatose), Sang **13**:1, 1939.

408. Giordano, G.: I nostri risultati nel trattamento radiante del linfogranuloma, Radiol. med. **26**:429, 1939.

between 21 and 30). The average treatment consisted of administration of 250 r at a time. Resistant tumors were treated with radium. For cases of diffuse involvement, "superteleroentgen therapy" was employed, with irradiation of the whole body for two hours at intervals of four or five days, 25 r being used at each treatment. The results appear best when the treatment is given early in the course of the disease. The duration of life in Giordano's series was more than three years in 45 cases and more than five years in 21 cases.

Craver [409] notes that Hodgkin's disease, lymphosarcoma and leukemia in children under 15 years of age have many points in common with the conditions in adults. Leukemia is nearly always acute and rapidly fatal and cannot be treated with roentgen therapy. For children with Hodgkin's disease the prognosis for palliation and length of survival is better than with lymphosarcoma or leukemia.

Marcellus [410] reports the curious coincidence of varicella and herpes in a patient with Hodgkin's disease.

In Randall's [411] case of Hodgkin's disease, extensive abdominal growths with deepening jaundice followed seven years after mediastinal involvement. The mediastinal glands became hyalinized. Rae's [412] patient, a man of 51, had intracranial deposits, convulsive seizures and an irregular temperature not characteristic of the Pel-Ebstein syndrome. There was marked pruritus. Browder and DeVeer [413] described 6 patients in whom lymphomatoid lesions involved the epidural space. These included lymphosarcoma (small and large cell types); giant follicular lymphadenoma; reticulum cell sarcoma; Hodgkin's disease, and multiple myeloma.

In Bomze and Kirschbaum's [414] case a 12 year old boy died of malignant thymoma (lymphosarcoma). There was no involvement of lymph glands and no leukemic infiltration of the other organs, and the blood picture was not abnormal. The tumor was radiosensitive, but death was caused by compression of the trachea and heart.

409. Craver, L. F.: Lymphomas, Leucemias and Allied Disorders in Children, J. Pediat. **15**:332, 1939.

410. Marcellus, M. B.: Hodgkin's Disease with Herpes Zoster and Varicella, Northwest Med. **38**:279, 1939.

411. Randall, E., Jr.: Internal Hodgkin's Disease, Texas State J. Med. **34**: 751, 1939.

412. Rae, A. S. L.: Clinical Record: A Case of Hodgkin's Disease with Cutaneous and Cerebral Manifestations, Edinburgh M. J. **46**:400, 1939.

413. Browder, J., and DeVeer, J. A.: Lymphomatoid Diseases Involving the Spinal Epidural Space: A Pathologic and Therapeutic Consideration, Arch. Neurol. & Psychiat. **41**:328 (Feb.) 1939.

414. Bomze, E. J., and Kirshbaum, J. D.: Lymphosarcoma of Mediastinum (Malignant Thymoma): A Clinical and Pathological Study with Case Report of a Child, J. Lab. & Clin. Med. **24**:928, 1939.

Dyes [415] and Horster [416] present cases of Hodgkin's disease associated with pregnancy. Taylor and De Ome [417] found that feeding wheat germ oil to chickens had no appreciable effect on the incidence, type or age of onset of lymphomatosis.

For Hodgkin's disease, Gilbert [418] recommends roentgen therapy only when there is a specific indication, and such therapy should be repeated only when necessary. He deprecates the so-called maintenance or prophylactic treatment as superfluous or even detrimental. Radium may produce a symptomatic remission of Hodgkin's disease, with reduction in size of deep-seated lymph nodes in the chest. Sayago [419] found that 160 mg. of radium at a distance of 6 to 7 cm. from the skin was a sufficiently strong source of radiation to accomplish excellent results. The cutaneous lesions of lymphoblastoma may be treated with irradiation (Pett [420]).

In Blatt and Page's [421] patient (a 38 year old man), a lymphosarcomatous mass involved the kidneys, renal vessels, ureters, abdominal aorta, inferior vena cava and adrenal glands. Hypertension (systolic blood pressure, 204 mm.; diastolic, 110 mm.) was a marked symptom and probably was the result of constriction of the renal arteries simulating the production of hypertension by the Goldblatt clamp.

In 5 cases of follicular lymphoblastoma described by Mayer and Thomas,[422] 2 patients showed changes limited strictly to the follicles, but in 1 of these the disease ran a malignant clinical course. Three of the patients showed invasion of the pulp by germinal center cells; in 2 of these the condition ran a malignant clinical course, while the third responded well to roentgen therapy. Four other cases are described in which there were general or local lymphadenopathy, splenomegaly (tumor cells in malpighian bodies), lymph nodes showing diffuse

415. Dyes, O.: Lymphogranulomatose und Schwangerschaftsunterbrechung, München. med. Wchnschr. **86**:605, 1939.

416. Horster, H.: Lymphogranulomatose und Schwangerschaft, Deutsche med. Wchnschr. **65**:680, 1939.

417. Taylor, L. W., and De Ome, K. B.: Failure of Wheat Germ Oil to Prevent Lymphomatosis in Chickens, J. Am. Vet. M. A. **95**:73, 1939.

418. Gilbert, R.: Radiotherapy in Hodgkin's Disease (Malignant Granulomatosis): Anatomic and Clinical Foundations; Governing Principles; Results, Am. J. Roentgenol. **41**:198, 1939.

419. Sayago, C.: Radium Therapy in Hodgkin's Disease: Report of a Case, Am. J. Roentgenol. **42**:888, 1939.

420. Pett, R. G.: Irradiation of Cutaneous Manifestations of Lymphoblastoma, Pennsylvania M. J. **42**:387, 1939.

421. Blatt, E., and Page, I. H.: Hypertension and Constriction of Renal Arteries in Man: Report of Case, Ann. Int. Med. **12**:1690, 1939.

422. Mayer, S., Jr., and Thomas, H. M., Jr.: Follicular Lymphoblastoma and Related Form of Lymphosarcoma, Bull. Johns Hopkins Hosp. **64**:315, 1939.

infiltration with lymphoblastic cells and a normal blood picture except for a moderate degree of anemia and a rapidly fatal course. These conditions constitute a separate syndrome.

LEUKEMIA

Biologic and Etiologic Aspects.—Forkner [423] summarizes the hematologic criteria in the differentiation of acute leukemias as follows: 1. The dominant leukocytes (85 per cent) are of uniform and immature type. 2. Leukocytosis may be absent, and leukopenia with fluctuations in the count may characterize the disease. 3. Thrombopenia is present. 4. Prolonged coagulation and bleeding times are observed. 5. There is rapidly developing anemia. The supravital technic is of aid in the diagnosis of monocytic cells. In cases of aleukemic myelogenous leukemia, roentgenograms of the skull, pelvis and femurs may show multiple erosions.

In a series of 20 cases of myelogenous and lymphatic leukemias, Davis and Fitz-Hugh [424] found an incidence of 35 per cent achlorhydria after administration of alcohol and histamine. Of the 20 patients, 7 had a smooth tongue, and in 4 the papillae were few. There was no correlation between achlorhydria, glossitis, anemia and neurologic disturbances in the group. Liver therapy appeared to have no effect on the anemia of these patients.

Moon [425] suggests the classification of leukemic and related conditions on the basis of (1) lymphoid, myeloid or reticuloendothelial ("retothelial") reaction; (2) the presence or absence of abnormal numbers of the pathologic cells in the blood, and (3) the presence of the same type of cell somewhere in the body.

An anonymous author,[426] in evaluating Engelbreth-Holm's [427] review (with an extensive bibliography) on leukemia, summarizes the available data as follows. The predisposing factors in cases of leukemia appear to be heredity, an external environmental factor (irritation) and a virus. While about 25 human families are known in which more than 1 case of leukemia occurring in near relatives has been recorded, pure strains of mice have been bred in which the incidence of leukemia was

423. Forkner, C. E.: Monocytic Leukemia and Subleukemic (Aleukocythemic or Aleukemic) Leukemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 126.

424. Davis, C. L., and Fitz-Hugh, T.: Achlorhydria in the Leukemias, Am. J. M. Sc. **197**:763, 1939.

425. Moon, V. H.: Practical Classification of Leukemic and Related Conditions, Am. J. Clin. Path. **9**:100, 1939.

426. Is Leukaemia a New Growth? editorial, Brit. M. J. **2**:1147, 1939.

427. Engelbreth-Holm, J.: Ergebnisse der Leukoseforschung der letzten Jahre, Ergebn. d. inn. Med. u. Kinderh. **56**:267, 1939.

90 per cent. In other strains the disease has been bred out so that it appears in only about 1 per cent. Radium, roentgen rays, tar and carcinogenic hydrocarbons have been reported as causing leukemia. In fowls, spontaneous leukemias can be transmitted to healthy birds by cell-free filtrates, and the virus acts much more rapidly than irritants. Sarcoma and leukemia have been produced by the same filtrable agent.

Jackson [428] points out that leukemia in individual cases may deviate sharply from the classic type and that other pathologic conditions, some of them curable, may give rise to a leukemoid blood picture. In 2 cases of lymphatic leukemia, in 1 of nine and in the other of twelve years' duration, there were very few symptoms. McGavran's case, in which there was leukemia of at least twenty-five years' duration, is cited. Sudden death from massive hemorrhage may occur from myelogenous leukemia in patients who are otherwise progressing satisfactorily. Aleukemic leukemia without characteristic physical findings or with symptoms of arthritis or acute abdominal disease may make the diagnosis difficult. Dramatic remissions may occur during the course of the disease. Miliary tuberculosis, carcinoma and myelosclerosis with myeloid metaplasia may give rise to leukemoid blood pictures.

Tissue autolysis with production of leukemia in chickens, dogs, monkeys, hogs, goats and sheep was induced by intravenous injection of living and heat-killing species of paratyphoid and typhoid bacilli and by injection of freshly emulsified, desiccated and autolyzed homologous tissues in the chicken, dog, monkey and goat. Benzene, phenol, xylene and suboxidation were effective in the chicken. Leukemia is considered as due to self-perpetuating tissue autolysis (Emmel [429]).

A paper of unusual interest in connection with the causation of leukemia is that of Wearn, Miller and Heinle.[430] These authors found that there is a substance in the urine of patients with leukemia which, when extracted by adsorption on kaolin (purified native hydrated aluminum silicate) from acid solution and eluted with alcohol, produces, on injection into guinea pigs, changes in the hemopoietic organs suggestive of the type of leukemia from which the urine was taken. Thus, there were marked hyperplasia of the bone marrow and metaplasia of myeloid cells in other parts of the reticuloendothelial system when the urine of patients with myelogenous leukemia was used, but when that

428. Jackson, H., Jr.: The Protean Character of the Leukemias and of the Leukemoid States, New England J. Med. **220**:175, 1939.

429. Emmel, M. W.: The Nature of Leukemia: A New Fundamental Principle Leading to the Development of Specific Disease, J. Am. Vet. M. A. **46**: 316, 1938.

430. Wearn, J. T.; Miller, F. R., and Heinle, R. W.: Proliferation of the Reticulo-Endothelial System Induced by Extracts of Urine from Patients with Leukemia, Tr. A. Am. Physicians **54**:278, 1939.

from patients with lymphatic leukemia or multiple myeloma was injected hyperplasia of the lymphoid elements was found. Extracts from urine of normal persons or of urine from patients with several other diseases did not produce this hyperplasia. As the extracts retained their activity after submission to a p_H of 1.5 and after boiling for five minutes, the authors conclude that the active substance probably was not a virus.

In 19 cases of chronic or subacute myelogenous or lymphatic leukemia, Morelli and D'Ambrosio [431] found that the indirect van den Bergh reaction was positive, the icteric index above normal, the resistance of the red blood cells moderately increased and, frequently, the urobilin content of the urine increased. Since all these findings agree with an increased hemolytic process, the authors advance the hypothesis that the anemia associated with leukemia is a hemoclastic phenomenon. It is not due to an aplastic process but to increased hemolytic activity of the spleen, profoundly altered by the lymphatic or myeloid metaplasia of the splenic tissue. The endocrine, leukopoietic and metabolic disturbances common to dysthyroidism and leukemia suggest to Marques [432] a common pathogenic factor for the two conditions. Lesions of the thyroid of the type of colloidal goiter were observed in 2 cases at autopsy.

Gerundo,[433] who favors the virus theory of leukemia, views the condition as a hyperplastic process involving the hemopoietic organs. Leukopenia is explained as representing a hyperfunction of the inhibitory action of the spleen on the growth and delivery of cells from the bone marrow and the hemohistioblastic nests.

Israëls [434] points out that lymphatic leukemia may exist in the absence of some classic signs but that lymphocytosis of the bone marrow (on sternal puncture) is diagnostic. Hynes's [435] observations bear this out, especially in the diagnosis of leukemia in the absence of peripheral leukocytosis. In the presence of leukemia the marrow is extremely cellular, with a great increase in the number of primitive leukocytes and a "maturation defect" in the red blood cells resulting in macrocytosis. The latter process differs from that in cases of pernicious anemia in that there is no premature hemoglobinization of the erythroblasts.

Voth [436] points out that it is often difficult to differentiate between granulocytopenia and aleukemic leukemia. There is often a marked

431. Morelli, A., and d'Ambrosio, L.: Il ricambio emoglobinico nelle leucemie, Haematologica **20**:253, 1939.

432. Marques, A.: A glandula tiroide e as leucemias, Jorn. dos clin. **20**:17, 1939.

433. Gerundo, M.: Acute Leukemia and Erythremia, J. Kansas M. Soc. **40**: 460, 1939.

434. Israëls, M. C. G.: Lymphatic Leukaemia: Value of Sternal Puncture in the Diagnosis of Atypical Cases, Brit. M. J. **2**:1132, 1939.

435. Hynes, M.: Sternal Puncture, Lancet **1**:1373, 1939.

436. Voth, G.: Granulocytopenie und Leukämie, Folia haemat. **62**:184, 1939.

discrepancy between the state of the cells in the blood stream and in the bone marrow. Granulocytopenia and aleukemic leukemia may be the first stage in a process affecting the bone marrow, which in some persons evolves into the second stage, acute myeloblastic leukemia.

Scott [437] characterizes as leukopenic myelosis a form of aleukemic leukemia which is marked by progressive anemia, a hemorrhagic tendency and liability to necrotic angina. An acute, a subacute and a chronic form are encountered. On sternal puncture a preponderance of primitive myeloid cells, mostly myeloblasts, is observed, with occasional hyperplasia of the erythropoietic tissues. There may be terminal leukocytosis. The anemia may be of the orthochromic or the hyperchromic type, with reticulocytosis and erythroblastosis at times. Thrombopenia may indicate a bad prognosis.

Of 86 patients with leukemia (39 with myelogenous and 47 with lymphogenous leukemia) treated at the Johns Hopkins Hospital (1926 to 1938), Wintrobe and Hasenbush [438] found that 61.5 per cent of the first group and 83 per cent of the second were men. The onset in 72 per cent of the former group occurred between the ages of 30 and 59 years; in 61.7 of the latter group it occurred between the ages of 50 and 69 years. Unexplained polymorphonuclear leukocytosis may be the initial abnormality in cases of myelogenous leukemia, while only one third of the patients with lymphogenous leukemia showed early unexplained leukocytosis. Patients of this type showed slight anemia more frequently than did the group with myelogenous leukemia. The interval from the initial symptom to the time that medical aid was sought was two to five years for patients with myelogenous leukemia and one and one-half to two and one-half years for those with lymphatic leukemia. Infection was more common in the latter type, and it did not produce symptoms of remission in either type. Solution of potassium arsenite U.S.P. was ineffective in cases of lymphogenous leukemia, and while it was of value in cases of the myelogenous type, it was less effective than roentgen therapy.

Leukemoid reactions of the myeloid type were studied by Heck and Hall.[132] These include pyogenic infections, subacute bacterial endocarditis, tuberculosis, hemolytic anemia, pernicious anemia, polycythaemia vera, chronic lymphatic leukemia, Hodgkin's disease, essential thrombopenia, erythroblastic anemia, acute loss of blood, severe anemia, granulocytopenia, metastases to bone marrow, multiple myeloma, osteosclerosis,

437. Scott, R. B.: Leukopenic Myelosis, Proc. Roy. Soc. Med. **32**:1429, 1939.

438. Wintrobe, M. M., and Hasenbush, L. L.: Chronic Leukemia: The Early Phase of Chronic Leukemia, the Results of Treatment and the Effects of Complicating Infections; a Study of Eighty-Six Adults, Arch. Int. Med. **64**:701 (Oct.) 1939.

diabetic coma and certain chemical poisonings. In these conditions immature bone marrow cells may be noted in the blood stream at times. The authors state that in most of the cases studied differentiation from leukemia could be made on the basis of clinical observations. Leukocyte counts above 100,000 per cubic millimeter were observed rarely in conditions other than chronic forms of leukemia, while many leukemic patients had counts which fell within or below the normal range. Approximately 40 per cent of all patients with acute leukemia and 10 per cent of all patients with chronic leukemia seen at the Mayo Clinic from 1928 to 1933 inclusive had leukocyte counts below 10,000 cells per cubic millimeter.

The special aspects of leukemia in children are discussed by Edward,[439] Booth and Rembolt[440] and Jelke[441] (acute lymphatic leukemia in unioval twins).

Experimental Leukemia in Animals.—The work of Kirschbaum and Strong[442] is significant in throwing some light on the nature of leukemia and the leukemic "soil" in susceptible subjects. In a group of mice (known as the F strain) inbred for twelve years (30 generations), enlarged spleens, lymph nodes or thymus glands were noted in over 200. Of the last 22 animals over 6 months of age which were killed or which died, 10 had either leukemia or mediastinal lymphosarcoma. In 17 cases of spontaneous leukemia and lymphosarcoma, both myelogenous and lymphatic leukemia, as well as leukemia of other types, developed. It was possible to transmit these to 295 mice of the F strain by subcutaneous or intraperitoneal inoculation of cells. Each type of inoculated cell bred true to type, suggesting proliferation of the introduced cells rather than transformation of reticuloendothelial or other mesenchymal cells. The neoplastic nature of the leukemic cells was evidenced by primary tumor formation followed by systemic leukemia, except after intraperitoneal injection of the cells, in which case the tumor phase was absent in some animals. Leukemic cells showed a wide degree of cytologic variation, and there appeared to be no specific cytomorphologic criteria for malignancy. Leukemic cells frequently had characteristics of normal young cells.

439. Edward, D. G. F.: Leukaemia in Children, Clin. J. **68**: 100, 1939.

440. Booth, M., and Rembolt, R. R.: Leukemia in Childhood: Evaluation of Present Status of Problem with Particular Reference to Study of Cases Treated at University of Minnesota Hospitals from 1930 to 1938, Journal-Lancet **59**:216, 1939.

441. Jelke, H.: Acute Lymphatic Leukemia in Uni-Oval Twins: I. Etiology, Acta pædiat. **27**:87, 1939.

442. Kirschbaum, A., and Strong, L. C.: Leukemia in the F Strain of Mice: Observations on Cytology, General Morphology and Transmission, Am. J. Cancer **37**:400, 1939.

MacDowell, Potter and Taylor [443] found that leukemic cells became more virulent after a long series of transfers from one animal to another. However, mice naturally susceptible to these highly virulent cells could be rendered resistant to these cells by intraperitoneal injection of graduated, increasing doses of the virulent cells or by intraperitoneal injection of a saline suspension of liver cells of these immunized mice or of embryonic tissue or normal liver suspensions from a special strain of mice. The immunized hosts, however, were still susceptible to the development of spontaneous leukemia.

Barnes and Sisman [444] studied myelogenous leukemia in mice, comparing it with nonmalignant extramedullary myelopoiesis. In the latter condition the abnormalities associated with malignant disease are absent, and all stages in the development of both white and red blood cells are present, contrasting with the predominance of immature myeloid cells in the presence of leukemia. Parenteral administration of suspensions of B. coli stimulates extramedullary hemopoiesis in rats. Exposure of mice with mammary tumors to small doses of roentgen rays did not produce myelogenous leukemia, and it failed to increase the extent of nonmalignant extramedullary myelopoiesis.

In mice, susceptibility plays an important part in the transmission of leukemia. In Schweitzer and Furth's [445] experiments there was a dominance in the inheritance of susceptibility in hybrids between susceptible and nonsusceptible stocks. The duration of the illness and the anatomic characteristics of the leukemia were not modified by the genotype of the host. Lewis [446] described a transplantable monocytoma in a mouse into which dibenzanthracene had been injected. Living cells were necessary to transmit the tumor, there being no evidence of a virus or of infectious organisms.

Furth [447] studied a spontaneous mouse tumor composed of monocytes. The morphologic structure of the cells and the microscopic appearance of the lesions were similar to those of neoplasms formed by histiocytes in the human being. Malignant histiocytes were necessary

443. MacDowell, E. C.; Potter, J. S., and Taylor, M. J.: Influence of Transplantation upon Immunological Properties of Leukemic Cells, Proc. Nat. Acad. Sc. **25**:416, 1939.

444. Barnes, W. A., and Sisman, I. E.: Myeloid Leukemia and Nonmalignant Extramedullary Myelopoiesis in Mice, Am. J. Cancer **37**:1, 1939.

445. Schweitzer, M. D., and Furth, J.: Susceptibility to Transmitted Leukemia Occurring in Pure Bred and Hybrid Mice, Am. J. Cancer **37**:224, 1939.

446. Lewis, M. R.: A Transmissable Monocytoma of the Mouse, Am. J. Cancer **36**:34, 1939.

447. Furth, J.: A Neoplasm of Monocytes of Mice and Its Relation to Similar Neoplasms of Man, J. Exper. Med. **69**:13, 1939.

to transplant the tumor, and attempts to transmit the disease with cell-free material were unsuccessful.

Kabat [448] observed a polysaccharide in tumors produced by a virus causing fowl sarcoma and leukosis. It was similar in its chemical properties and in its behavior toward a pneumococcus enzyme preparation to the substance isolated from vitreous humor, the umbilical cord, the synovial fluid and the mucoid hemolytic streptococcus.

Stern and Kirschbaum [449] isolated by ultracentrifugalization of saline extracts of leukotic fowl bone marrow a macromolecular material which contained the active virus. The substance contained about 9.5 per cent nitrogen, as well as thymonucleic acid, hemin, cytochrome oxidase and catalase, although these enzymes may have been present in associated substances.

Marchal, Paturel, Guérin and Guérin [450] noted that there was no change or a slight increase in globulin in hens inoculated with leukemia. After immunization there was a 50 per cent increase in the serum globulin concentration above normal.

Jármai [451] found that, while tissue emulsions of mouse carcinoma and mouse and rat sarcoma were inactivated by small doses of roentgen rays, erythroleukotic and sarcomatous tissue from fowls resisted much larger doses, suggesting that the causative agent is apparently of the nature of an enzyme.

Furth [452] has published an excellent review of 96 articles on experimental leukemia in birds and mammals. Among the agents which have produced leukemia are roentgen rays, benzene, indol, methylcholanthracene, estrogens and benzopyrene. Storti and Brotto [453] found that the substance which produces fowl leukemia on injection localizes primarily in the bone marrow, where it acts on the erythroblastic tissue. Some of the substance is taken up in the liver and spleen. After injection, the substance disappears rapidly from the blood stream but reappears after

448. Kabat, E. A.: A Polysaccharide in Tumors Due to a Virus of Leucosis and Sarcoma of Fowls, J. Biol. Chem. **130**:143, 1939.

449. Stern, K. G., and Kirschbaum, A.: On the Nature of the Agent Causing Leucosis in Fowls, Science **89**:610, 1939.

450. Marchal, S.; Paturel, L.; Guérin, M., and Guérin, P.: Recherches sur la teneur en protides du sérum de poulis inoculées avec une leucemie ou avec des sarcomes, Compt. rend. Soc. de biol. **131**:213, 1939.

451. Jármai, K.: Ueber die Röntgenresistenz des Agens der übertragbaren Tiergeschwülsten und zur den Agenzien der übertragbaren Hühnersarkome, Arch. f. wissensch. u. prakt. Tierh. **74**:67-74, 1939.

452. Furth, J.: Experimental Leukemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 105.

453. Storti, E., and Brotto, M.: Ueber die Pathogenese der übertragbaren Hühnerleukämie, Folia haemat. **63**:1, 1939.

a period of three days. Extramedullary leukemic foci are metastatic and are not the result of the action of the leukemic virus on local hemohistioblasts. The authors consider fowl leukemia to be neoplastic.

Hester and Graham [454] have described lymphatic leukemia in a pig 3 months old. There were splenomegaly, lymphadenopathy, 18,250 lymphocytes per cubic millimeter of blood and invasion of the organs by lymphocytes.

LEUKEMIA: CHEMICAL AND PATHOLOGIC PICTURE

Data as to the nature of myeloblasts, lymphoblasts and "acute splenic tumor cells" have been accumulated by Rich, Lewis and Wintrobe.[455] By analyzing the motions of the cells in vitro with the motion picture technic it was found that the lymphoblast and the myeloblast have a different behavior and that the splenic tumor cell resembles the former. In cases of leukemia the behavior of the cells is the same as that of the stem cell which is involved, whether this is a lymphoblast or a myeloblast. Lymphoid activity with lymphadenopathy and splenomegaly characterized the response to injection of foreign protein, suggesting a possible relation of the lymphocyte to antibody formation.

Hirschberg [456] studied phagocytosis, the sedimentation rate and the occurrence of bacteria in the blood in 20 cases of different types of leukemia. She found that the phagocytic power of leukemic blood was decreased, only from 30 to 70 per cent of the mature neutrophils showing phagocytic tendencies as compared with 96 per cent in the controls. In the leukemic cells the range was from 2.6 to 38.2 bacteria per cell (controls, 18). The blood of subjects with the chronic condition was relatively free from bacteria, and in those with the acute condition in whose cases positive bacteriologic observations were made the infection appeared to be superimposed on the leukemia. In 10 of the patients the sedimentation rate was normal; in the others, slow or rapid.

Forconi [457] advocates puncture of both the spleen and the bone marrow as a check on the accuracy of the diagnosis and as a means of determining the involvement of the organs in a leukemic process.

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454. Hester, H. R., and Graham, R.: Lymphocytoma or Lymphoid Leucemia in a Pig, Cornell Vet. **29**:334, 1939.

455. Rich, A. R.; Lewis, M. R., and Wintrobe, M. M.: The Nature of the Acute Splenic Tumor Cell, as Revealed by Comparative Motion Picture Studies of Cells of the Spleen, Lymph Nodes, Bone Marrow and Leukemic Blood, Tr. A. Am. Physicians **54**:188, 1939.

456. Hirschberg, N.: Phagocytic Activity in Leukemia, Am. J. M. Sc. **197**: 706, 1939.

457. Forconi, A.: Pour confirmer l'importance des ponctions de la rate et de la moelle osseuse dans les myéloses érythrémiques sub- et aleucémiques, Sang **13**: 380, 1939.

Kempner [458] studied the metabolism of leukemic lymphocytes in a Warburg apparatus. Myeloblasts and lymphoblasts have a purely oxidative metabolism, differing from the mature forms, and do not form lactic acid under aerobic conditions. Anaerobic glycolysis of myeloblastic blood was seven and six-tenths times that of normal blood, and the respiratory rate was forty-seven times greater. The respiratory quotient of myeloblasts measured in air is 0.75. Aerobic glycolysis in more mature leukocytes is a symptom of senility and dying. Both myeloblasts and lymphoblasts have the metabolism of normal cells and not of cancer cells.

Rin,[459] in studying the metabolism of leukocytes in a Warburg apparatus, found the respiratory and glycolytic rate to be increased above normal in the presence of both chronic myelogenous and chronic lymphatic leukemia. The author concludes that the metabolic type is that of fetal cells rather than that of malignant tumor tissue. The metabolism of immature leukocytes was active, that of myeloblasts being greater than that of lymphoblasts. The author sees no supportive evidence for classifying leukemia with malignant tumors.

Kuzuya [460] found that of the total protein content the residual nitrogen content of the blood plasma was similar in acute, subacute and chronic myelogenous leukemia. Either the values for fibrinogen and for total proteins of the blood plasma were low normal or the fibrinogen content was increased in amount while the plasma residual nitrogen was increased. Fibrinogen increased in amount after roentgen therapy administered over the spleen.

Büchmann [461] found that the iron content of the serum was normal or increased in the presence of chronic leukemia, but in the presence of myeloblastic leukemia the serum iron decreased when the body temperature became elevated. The blood of patients with myelogenous leukemia gave a microchemical "nucleal" reaction for thymonucleic acid.

Voit and Borgard [462] found this reaction to be direct without previous hydrolysis. Vogelensang [233] found that the zinc content of the leukocytes is higher than that of the red blood cells in cases of leukemia. Normally about 90 per cent of the zinc is in the erythrocytes.

458. Kempner, W.: Nature of Leukemic Blood Cells as Determined by Their Metabolism, J. Clin. Investigation **18**:291, 1939.

459. Rin, Mo-Sei: The Metabolism of Leukocytes in Leukemia, Acta haemat. japon. **2**:351, 1938.

460. Kuzuya, K.: Partition of Blood-Plasma Protein and Residual Nitrogen, Ztschr. f. klin. Path. u. Hämatol. **6**:269, 1937.

461. Büchmann, P.: Die Bewegung des Serumeisens bei Myeloblastenleukämien, Klin. Wchnschr. **18**:281, 1939.

462. Voit, K., and Borgard, P.: Zur Nuclealreaktion des myeloischen Blutbilds, Klin. Wchnschr. **18**:754, 1939.

Stodtmeister and Büchmann [463] consider that iron deficiency accounts for the anemia occurring in the course of leukemia. The iron content of the serum is independent of the number of erythrocytes or leukocytes. A fall in the level of serum iron accompanies progressive deterioration and is a sign of poor prognosis. An increase in serum iron accompanies a remission induced by roentgen therapy.

By the use of radioactivated phosphorus in the form of disodium hydrogen phosphate (Na_2HPO_4) the phosphorus metabolism in 2 cases of chronic myelogenous leukemia was studied by Tuttle, Scott and Lawrence.[464] While the turnover of phosphorus in the red blood cells is rapid, the white blood cells retain this substance for a long time. One patient had retained 80 per cent. As 26 per cent of the cells in 1 patient and 33 per cent of those in the other were immature, it was not possible to say whether the handling of phosphorus by the leukocytes was normal (Lawrence and Scott [465]).

De Lucia and Morelli [466] found that in patients with leukemia all blood phosphorus fractions except the inorganic ones are increased. After administration of vitamin B_1 all are slightly decreased. The same is true of the erythroblastoses. With anemias the various blood phosphorus fractions show values lower than normal. There is no appreciable difference in pernicious anemia and secondary anemia, and vitamin B_1 causes no change. The authors conclude that these variations of the level of blood phosphorus are not due to parallel variations in the number of blood cells but are the result of a direct action of vitamin B_1 on the blood phosphorus group, which is affected by various factors, including the action of the reticuloendothelial system.

Hemmeler [150] found high values for serum iron in cases of pernicious anemia (200 micrograms per hundred cubic centimeters); increased amounts are noted in cases of hemolytic anemia, hemochromatosis, catarrhal jaundice and leukemia (normal values: for males, 100 to 130 micrograms, and for females 80 to 100 micrograms, per hundred cubic centimeters).

The phosphatase values of whole blood, serum and urine were found by Iwatsuru and Nanjo [467] to be increased in the presence of chronic

463. Stodtmeister, R., and Büchmann, P.: Die Bedeutung des Serumeisenspiegels für die Beurteilung Leukämiekranker, Klin. Wchnschr. **18**:1365, 1939.

464. Tuttle, L. W.; Scott, K. G., and Lawrence, J. H.: Phosphorus Metabolism in Leukemic Blood, Proc. Soc. Exper. Biol. & Med. **41**:20, 1939.

465. Lawrence, J. H., and Scott, K. G.: Comparative Metabolism of Phosphorus in Normal and Lymphomatous Animals, Proc. Soc. Exper. Biol. & Med. **40**: 694, 1939.

466. DeLucia, P., and Morelli, A.: Azione della vitamina B_1 sul quadro del P ematico in alcune emopatie, Haematologica **20**:281, 1939.

467. Iwatsuru, R., and Nanjo, K.: Studien über Phosphatase: VIII. Ueber die Phosphatasenaktivität des Blutes, Serums und Harns bei chronicher myeloischer Leukämie, Biochem. Ztschr. **300**:422, 1939.

myelogenous leukemia. After roentgen therapy the phosphatase content of the serum and, later that of the urine increase, suggesting that the myeloid leukocytes are sources of phosphatase in the blood and that when they are destroyed the phosphatase is eliminated in the urine.

Albers [468] did not note any deviation from normal in the levels of serum phosphatase in 21 cases of leukemia, but the values rose after roentgen therapy. Koster [469] reports increased phosphastase in the feces in the presence of leukemia.

Keilhack [45] found large amounts of globulin but less albumin than normal in the femur marrow of a patient with chronic myelogenous leukemia. The level of prothrombin in the blood was found to be slightly reduced in cases of acute leukemia by Scanlon, Brinkhous, Warner, Smith and Flynn.[309]

In cases of leukemia Kreuzwendedich von dem Borne [470] found that the vitamin C content of the blood was greatly increased, but there was a possibility that some nonspecific reducing substance might have complicated the test. In the presence of clinical evidence of vitamin C deficiency, administration of ascorbic acid is without effect.

Spellberg and Keeton [471] found increased utilization of ascorbic acid in cases of leukemia.

Pennetti [35] found that the oxalic acid content of the blood was increased in certain cases of leukemia, probably as a result of hepatic insufficiency.

Graff [472] found that the ratio of cholesterol to noncholesterol fractions in the blood serum in cases of leukemia was very high, owing to the extremely low values for the noncholesterol fraction, although the cholesterol fraction itself was lower than normal.

Gingold [473] found that the value for blood histamine is normally about 0.1 gamma per cubic centimeter, but with chronic myelogenous leukemia the value may be one hundred times this amount. The histamine content of the blood in cases of lymphatic leukemia is not elevated

468. Albers, D.: Die Serumphosphatase bei myeloischer und lymphatischer Leukämie, Ztschr. f. d. ges. exper. Med. **105**:155, 1939.

469. Koster, L.: The Occurrence of Glycerophosphatase in the Feces, Nederl. tijdschr. v. geneesk. **82**:5856, 1939.

470. Kreuzwendedich von dem Borne, G. A.: Actual and So-Called Vitamin C Deficiency, Acta med. Scandinav. **99**:449, 1939.

471. Spellberg, M. A., and Keeton, R. W.: Excretion of Ascorbic Acid in Relation to Saturation and Utilization, with Some Diagnostic Implications, Arch. Int. Med. **63**:1095 (June) 1939.

472. Graff, U.: Untersuchungen über das Unverseifbare des menschlichen Serums, Biochem. Ztschr. **298**:179, 1938.

473. Gingold, N.: Un élément nouveau dans le diagnostic différentiel de la leucémie myéloïque chronique, Bull. Acad. de méd. de Roumanie **8**:382, 1939.

to this extent. Increase in oxidized glutathione was noted in cases of myelogenous leukemia, especially of the severe forms, by Weil, Aschkenazy and Caprin,[227] but this substance was reduced or absent in cases of lymphatic leukemia and of erythroblastosis. No parallelism was found between the glutathione content and the basal metabolic rate when correlated with the cholesterol content of the blood. In cases of myelogenous leukemia the concentration of total glutathione was 36.3 to 57.1 mg., that of reduced glutathione 35.5 to 53 mg. and that of oxidized glutathione 0.5 to 4.1 mg. per hundred cubic centimeters. In cases of lymphatic and monocytic leukemia the values were: total and reduced glutathione, 13.7 to 54.7 mg., and oxidized glutathione, 0 to 6.3 mg., per hundred cubic centimeters. In cases of erythroblastosis they were: total and reduced glutathione, 27.4 to 43.3 mg. per cent; oxidized glutathione, 0.

Kandel and Le Roy [474] found that the reduced glutathione content of the blood of normal persons was 33.28 ± 2.83 per cent and the total glutathione content 40.20 ± 2.58 per cent; in patients with pernicious anemia, 33.92 ± 1.5 per cent; in patients with erythroblastic anemia 22.9 and 29.8 per cent, and in patients with polycythaemia vera, 65.36 and 75.16 per cent. No definite correlation between the type of the disease and the glutathione content was evident, but there is a crude relation to the number of formed elements in the blood.

Schultz [80] found a high concentration of glutathione in the blood of a patient with myelogenous leukemia, and Malenkova [475] reported a similar finding, but the ratio of oxidized to reduced glutathione was below normal. The increased glutathione was found mostly in the leukocytes.

Grunke and Koletzko [476] found that while patients with renal disease, neoplasms and pulmonary inflammations secreted an increased amount of the substance (present in normal urine) which favors coagulation of "artificial" hemophilic blood, patients with disease of the liver, pernicious anemia, leukemia and agranulocytic angina secreted but little or none of the substance.

Clinical Data.—A type of acute leukemia in which there is nonsymptomatic hypertrophy of the thymus is described by Pierret, Chris-

474. Kandel, E. V., and LeRoy, G. V.: The Blood Glutathione in Hematologic Diseases, J. Lab. & Clin. Med. **24**:669, 1939.

475. Malenkova, K. M.: The Glutathione Content of the Blood in Leukemic Patients, Klin. med. **16**:1007, 1938.

476. Grunke, W., and Koletzko, T.: Studien über die Blutgerinnung mit besonderer Berücksichtigung der Hämophilie. Einfluss des Harnes auf die künstlich verzögerte (hämophilie-artige) Gerinnung des Plasmas, Ztschr. f. d. ges. exper. Med. **105**:46, 1939.

tiaens, and Popoff.[477] The tumor is usually sensitive to roentgen rays, and great care is necessary in the application of roentgen therapy. The authors suggest a study of the thymus before treatment in cases of leukemia, as well as a thorough study of the blood in any other case in which thymic tumor is discovered.

A patient with eosinophil leukemia was studied by Thomsen and Plum,[478] who found "a peculiar cell in the bone marrow (40%)." This cell, interpreted as the parent cell of the abnormal eosinophils of the blood, had a small, compact, often vacuolated nucleus, with colorless or faintly blue-staining cytoplasm with fine blue-green or eosinophil plaques or granules at the periphery. The disease terminated as myeloblast leukemia.

The relation of trauma and leukemia is discussed by Olovson[479] in reporting 2 cases (fracture; concussion). Of 67 similar cases in the literature, there were 40 of trauma to the splenic region and 8 of fracture of a bone. Considering the number of traumatized persons, traumatic leukemia is rare.

The subject is also treated by Yaguda and Rosenthal.[480]

An instance of the appearance of myelogenous leukemia in a young woman whose mother had died of the same disease fifteen years previously is cited by Laub.[481] The author postulates a hereditary rather than an incidental relation between the 2 cases.

Decastello[482] describes 6 cases of lymphatic leukemia in two generations of the same family. Except for 1 patient who showed symptoms in youth and in whom the disease was of fourteen years' duration, the incidence was between the ages of 40 and 50 years. Decastello feels that heredity may be a factor in leukemia.

Court[483] describes 2 cases of monocytic leukemia in childhood and reviews the cases reported previously. There is no clearcut clinical picture, and the diagnosis must be made from data obtained from the blood and the sternal marrow and by biopsy of material from the lymph nodes.

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477. Pierret, R.; Christiaens, L., and Popoff: L'hypertrophie du thymus au cours de la leucémie aiguë de l'enfant (à propos de trois cas), Arch. de méd. d. enf. **42**:5, 1939.

478. Thomsen, S., and Plum, P.: Eosinophilic Leukemia, Ugesk. f. læger **101**: 90, 1939; Acta med. Scandinav. **101**:116, 1939.

479. Olovson, T.: Trauma und Leukämie, Acta chir. Scandinav. **82**:63, 1939.

480. Yaguda, A., and Rosenthal, N.: Relation of Trauma to Leukemia, Am. J. Clin. Path. **9**: 311, 1939.

481. Laub, R.: Ueber familiäres Auftreten der Leukämie, Schweiz. med. Wchnschr. **69**:71, 1939.

482. Decastello, A.: Aspects of Familial Leukemia, Med. Klin. **35**:1255, 1939.

483. Court, D.: Monocytic Leukemia in Childhood, Arch. Dis. Childhood **14**: 231, 1939.

Unusual infiltration of the eyelids with lymphoid cells in a 65 year old man with aleukemic lymphatic leukemia was noted by Tooke.[484] The local lesion regressed with roentgen therapy (1,000 to both lids), but the systemic disease progressed.

A hemolytic leukemoid condition in a man 34 years of age with angina is described by Gingold and Comsa.[485] A syndrome of prostration, urinary incontinence, dyspnea, extreme pallor with an icteric tint, splenomegaly, severe anemia, marked leukocytosis (white blood cell count, 112,000 per cubic millimeter), hemoglobinuria, cylindruria and nitrogen retention appeared. The leukemoid reaction and hemolytic process may have been induced or aggravated by neoarsphenamine and quinine given intravenously and prontosil (now known as azosulfamide [N. N. R]; disodium 4 - sulfamidophenyl - 2′- azo - 4′- acetylamino - 1′- hydroxynaphthalene-3′,6′ disulfonate) given orally. The nonelevation of the uric acid and histamine content of the blood differentiated this condition from leukemia.

A case of leukemia is presented by Gandellini [486] in which a myeloid and a lymphatic leukemic picture coexisted from the onset. There was chronic evolution, and the disease did not respond to any form of treatment. The clinical and pathologic-anatomic pictures were considered typical of "mixed" leukemia.

A patient with congenital leukemia is described by Morrison, Samwick and Rubinstein.[487] The leukocyte count rose to 300,000 per cubic millimeter before death, the blood showing many atypical myeloblasts. Chloromatous tumors were present on the back and scalp, and small infiltrations were scattered over the body.

From a detailed study of a case, Bianchi [488] concludes that the essential histologic characteristics of acute erythremic myelosis are hyperplasia of the cells of the reticuloendothelial system with an exclusively erythroblastogenetic evolution and hyperplastic alterations of the secondary hemopoietic organs. Histioerythroblastic foci were demonstrated in the kidney, the adrenals, the myocardium and the testicles. These observations are interpreted as confirming the opinion of Di Guilelmo

484. Tooke, F. T.: Case of Aleukemic Lymphosis Involving Upper Lids with Pathologic Findings, Tr. Am. Ophth. Soc. **36**:368, 1938.

485. Gingold, N., and Comsa, G.: Anémie hémolytique aiguë grave avec tableau leucémoïde, consécutive à une angine traitée par divers agents chimiques; considérations pathogéniques, Sang **13**:517, 1939.

486. Gandellini, A.: Contributo allo studio delle leucemie miste, Haematologica **20**:83, 1939.

487. Morrison, M.; Samwick, A. A., and Rubinstein, R. I.: Congenital Leukemia with "Chloroma," Am. J. Dis. Child. **58**:332 (Aug.) 1939.

488. Bianchi, C.: Contributo clinico et anatomo-pathologico allo studio della mielosi erithremica acuta (mallatia di Di Guglielmo), Haematologica **20**: 213, 1939.

that acute leukemia and acute erythremia are analogous diseases with a common histogenetic foundation.

Wynn-Williams' [489] patient (a woman aged 32 years) had ulcerative tonsillitis, and the leukocyte count was 16,800 per cubic millimeter. Of these, 62 per cent were lymphocytes, and there was no reduction in the number of neutrophils. Later, immature cells appeared (premyelocytes?), and there was mild anemia. The blood returned to normal with recovery. Because of this fact the disease was interpreted as an unusual response to a virulent streptococcic infection, rather than leukemia.

In McDonald and Waugh's case,[490] postmenopausal bleeding was caused by leukemic (lymphatic) infiltration of the endometrium.

Fillis [491] describes the development of acute myelogenous leukemia in a 58 year old woman after trauma to the right kidney and nephrectomy for uncontrollable renal hemorrhage. Radium treatment of the uterus may have been one of the inciting factors.

In describing a case of diabetes mellitus and chronic lymphatic leukemia, Hart, Lisa and Riedel [492] conclude that the relation was probably fortuitous. The glycolytic rate was not abnormal. While the three types of leukemia are represented in reported cases, the lymphatic form is most common.

Two cases of chronic monocytic leukemia in women with marked cutaneous involvement are described by Freeman and Koletsky.[493] In both there were extensive discrete, nodular cutaneous lesions, which in 1 case became confluent and indurated, with a bullous, fungating surface. The lymph nodes in the first case showed but slight involvement, with diffuse infiltration of the bone marrow (nondestructive), spleen, adrenal glands, kidneys and pituitary. In the other case there were widespread bulky involvement of the lymph nodes with focal and nodular (destructive) lesions of the bone marrow and a normal liver and spleen but infiltration occurred in the nose, tonsils, thyroid, stomach,

489. Wynn-Williams, N.: Ulcerative Tonsillitis with Blood Count Simulating Lymphoid Leukaemia, Brit. M. J. **1**:1032, 1939.

490. McDonald, J. R., and Waugh, J. M.: Chronic Lymphatic Leukemia with Infiltration into Endometrium: Report of a Case, Proc. Staff Meet., Mayo Clin. **14**:465, 1939.

491. Fillis, B. E.: Severe Unilateral Hematuria in a Case of Acute Myelogenous Leukemia, J. Urol. **42**:57, 1939.

492. Hart, J. F.; Lisa, J. R., and Riedel, P. A.: Diabetes Mellitus Complicated with Lymphatic Leukemia: Report of Case with Autopsy, J. A. M. A. **113**: 1222 (Sept. 23) 1939.

493. Freeman, H. E., and Koletsky, S.: Cutaneous Lesions in Monocytic Leukemia: Report of Two Cases with Pathologic Study, Arch. Dermat. & Syph. **40**: 218 (Aug.) 1939.

lungs and pancreas. This case, in which leukopenia was present, may fall into the type of "reticuloendotheliosis" or of reticulum cell sarcoma.

Grayzel and Lederer [494] describe a case of leukemic myelosis (aleukemic myelogenous leukemia) in a 13 year old girl, in which metastatic calcification was observed at autopsy in the lungs, left atrium, adrenal glands, kidneys, thymus gland and some of the moderate-sized arteries.

Grier and Richter [495] describe the details of pregnancy coexisting with leukemia and analyze from the literature 28 cases of chronic leukemia and 25 cases of acute leukemia complicated by pregnancy. With acute leukemia the maternal mortality was 100 per cent within five weeks after delivery. With chronic leukemia many mothers lived at least two and one-half months, with a mortality of 51.7 per cent. The fetal mortality was 68 per cent in cases of acute leukemia and 37.1 per cent in cases of chronic leukemia. None of the babies had leukemia. The authors conclude that pregnancy should be avoided when leukemia is known to be present. Interference with pregnancy does not help the mother, and in the presence of acute leukemia shortens her life. The babies thus delivered are either premature or nonviable. In all except 1 of the cases of chronic leukemia the condition was myelogenous.

Tschopp's [496] case is a contribution to the effect of pregnancy on the course of leukemia. His patient went through one normal pregnancy without evident aggravation of the disease, but operative termination of a second pregnancy, which had been progressing uneventfully for four or five months, was followed by rapidly developing myeloblastic overgrowth (acute leukemia), with a fatal termination. As to the part played by the pregnancy, the operation or the previous roentgen therapy (the leukocyte count had fallen to 4,000 per cubic millimeter) there is room for speculation.

Treatment.—The prognostic significance of the presence or absence of myeloblasts in the blood stream is emphasized by Israëls.[497] Their presence is not of serious import if they disappear from the peripheral blood after roentgen therapy, but if they increase in number the outlook is grave. The myeloblastic transformation of the marrow parallels that of the blood. Treatment is effective when the relative number of immature forms decreases and the anemia improves. Israëls takes the view that roentgen therapy may be postponed in the presence of

494. Grayzel, D. M., and Lederer, M.: Metastatic Calcification: Report of Two Cases, Arch. Int. Med. **64**:136 (July) 1939.

495. Grier, R. M., and Richter, H. A.: Pregnancy with Leucemia: Case Report and Review of Literature, Am. J. Obst. & Gynec. **37**:412, 1939.

496. Tschopp, W.: Beitrag zur Frage der akuten Myeloblasenleukämie (Leukämie und Gravidität), Folia haemat. **61**:319, 1939.

497. Israëls, M. C. G.: Treatment of Chronic Myeloid Leukaemia: Importance of Myeloblast, Lancet **1**:317, 1939.

anemia provided that the progress of the disease and the condition of the patient do not require immediate irradiation therapy.

The so-called "spray method" of treating leukemia is favored by Harrison and Reeves [498] over the method of local treatment. Of 47 patients with leukemia of different types, 84 per cent of those treated with the spray method were living, as compared to 22 per cent who had local treatment and 56 per cent for whom the two methods were combined. This would suggest that the "local" method of treatment shortened the patients' lives. The authors consider that there is less danger of aplastic anemia with the spray method than with other methods, but its use is contraindicated in cases of aleukemic leukemia. Confirming previous authors, they feel that the total life span of the patient is not prolonged but that there is an added period of usefulness. While only 47 per cent of the 47 patients gave a history of previous infection, the authors consider that these observations lend weight to the infection theory of causation of leukemia.

Andrus and Holman [117] removed the spleen from a patient with some type of aleukemic leukemia. The patient lived for four months after the operation, without improvement.

The use of radioactivated phosphorus in the treatment of leukemia was tested by Lawrence, Scott and Tuttle.[499] The types of leukemia tested were lymphatic, monocytic and chronic and acute myelogenous. Radioactivated phosphorus in the form of sodium phosphate solution was given by mouth at irregular intervals of from one to nine days for prolonged periods. A fall in the number of leukocytes, occasionally preceded by a rise, was followed, however, by death. The changes in the tissues at autopsy were interpreted as not indicating untoward effects from administration of the material. The major portion of each dose of "labeled" phosphorus is absorbed during the first three days and is thereafter excreted in small amounts in both urine and feces, chiefly in the former. There is greater deposition of the activated phosphorus in bone marrow and bone than in other human tissues and, at least in leukemic mice, a relatively large amount in leukemic osseous and lymphomatous tissue (Lawrence and Scott [465]).

Brauner and Gottlieb [500] found that in the presence of leukemia and other conditions small doses of roentgen rays accelerate maturation of the granulocytes, increasing the number of polymorphonuclear cells in the bone marrow. There is a progressive decrease in the per cent of

498. Harrison, E. K., and Reeves, R. J.: Roentgen Treatment of Leukemia, with Report of Pregnancy in Case of Lymphatic Leukemia, Radiology **32**:284, 1939.

499. Lawrence, J. H.; Scott, K. G., and Tuttle, L. W.: Studies on Leukemia with Aid of Radioactive Phosphorus, Internat. Clin. **3**:33, 1939.

500. Brauner, R., and Gottlieb, F.: Les modifications du myélogramme au cours de la roentgenthérapie, Sang **13**:963, 1939.

cells in the immature stages, with an increase in the number of those in more mature stages. Large doses inhibit the growth of the marrow cells. The changes in bone marrow appear early, some effects being evident in eight minutes, with the maximum effect in twenty-four to forty-eight hours.

Bean, Vilter and Spies [501] found that ether-soluble pigments having the color of porphyrin in 25 per cent hydrochloric acid, similar in appearance to those found in the urine of pellagrins, appeared in the urine of patients with myelogenous leukemia as well as in that of healthy persons twelve hours after roentgen irradiation. They disappeared in forty-eight hours. Nicotinic acid administered before irradiation prevented excretion of the abnormal pigments but did not decrease the coenzyme content of the blood. Otherwise the blood codehydrogenases I and II decreased 60 to 90 per cent within twelve hours. A possible relation to "roentgen sickness" is postulated.

Bernard [502] found that colchicine given by mouth was therapeutically ineffective in cases of acute leukemia, but when given into the sternal marrow of a 5 year old boy with acute aleukemic leukemia it increased the degree of maturation of the leukocytes. Thus the leukoblastic cells of the marrow were reduced from 100 per cent to 41 per cent. There was no general improvement in the red blood cell picture or in the clinical condition, and the fatal evolution of the disease did not appear to be influenced.

MULTIPLE MYELOMA

Grosgurin [503] has published a review of 58 articles on multiple myeloma. An analysis of 40 cases of multiple myeloma was made by Batts.[504] Of the patients, 63 per cent were men; there was a family history of some type of neoplastic growth in 31 per cent of the cases; the average age was 53 years (range 28 to 73); the incidence was 1 case in 7,464 admissions to the hospital; a history of trauma was absent in 70 per cent of cases. The clinical history was not typical. The lesions were invariably multiple. The skull, spine, ribs, pelvis, shoulder girdle, humerus and femur were involved in decreasing frequency. The author states that Bence-Jones protein may be absent from the urine and that its presence is not always pathognomonic of the disease. While many

501. Bean, W. B.; Vilter, R. W., and Spies, T. D.: The Effect of Roentgen-Ray on the Blood Codehydrogenases I and II, Ann. Int. Med. **13**:783, 1939.

502. Bernard, J.: Leucémie aiguë. Essai de traitement par les injections intermédullaires de colchicine. Modifications médullaires et sanguines, Sang **13**:434, 1939.

503. Grosgurin, T. R.: Le myélome multiple, Sang **13**:30-65, 1939.

504. Batts, M., Jr.: Multiple Myeloma: Review of Forty Cases, Arch. Surg. **39**: 807 (Nov.) 1939.

types of blood picture were encountered, the most constant finding was iron deficiency anemia (severe in 23 per cent of cases). The leukocyte count varied from low to 15,500 per cubic millimeter. Plasma cells were reported in the blood in only 3 cases. Roentgen therapy relieves pain and prolongs life. (For nontreated patients the average duration of life after admission to the hospital was six months; for treated patients, twenty-three months.)

Jersild [505] found that of 27 patients with anticomplementary serum, 13 definitely and 5 probably had myelomatosis. The reaction was carried out after the serum had been heated to from 56 to 60 C. The globulin is increased in amount, and the coagulation temperature of the serum is often low.

In Ulrich's [506] case the values for blood protein and blood calcium were high, with normal or high values for serum phosphorus. Bence Jones protein was present in the urine.

Tarr and Ferris [507] report the twelfth and thirteenth cases in the literature in which multiple myeloma was accompanied by tumor-like deposits of amyloid in and about the joints. The amyloid was not abundant in the usual sites and frequently had an atypical staining reaction. Bence Jones substance was present in the urine. The involvement of the joints and muscles by amyloid masses simulated rheumatoid arthritis.

GAUCHER'S DISEASE, HAND-SCHÜLLER-CHRISTIAN DISEASE AND NIEMANN-PICK DISEASE

Schleussner and Schnee [508] summarize the present data about Gaucher's disease and describe a case of this condition in a 28 year old man. They conclude that in cases of well advanced involvement a persistent leukopenia, even in the presence of a high temperature and a fulminating infection, is a diagnostic feature not present with other splenomegalies.

The cerebroside in the spleen of a patient with Gaucher's disease was found by McConnell, Forbes and Apperly [509] to be kerasin. No phrenosin was present.

505. Jersild, M.: Diagnosing Myelomatosis with Complement Fixation, J. A. M. A. **113**:1119 (Sept. 16) 1939.

506. Ulrich, H.: Multiple Myeloma, Arch. Int. Med. **64**:994 (Nov.) 1939.

507. Tarr, L., and Ferris, H. W.: Multiple Myeloma Associated with Nodular Deposits of Amyloid in the Muscles and Joints and with Bence-Jones Proteinuria, Arch. Int. Med. **64**:820 (Oct.) 1939.

508. Schleussner, R. C., and Schnee, C. F.: Gaucher's Disease: A Brief Review of the Disease with Report of a Case in a Male, New York State J. Med. **39**: 1665, 1939.

509. McConnell, J. S.; Forbes, J. C., and Apperly, F. L.: Chemical Studies of a Gaucher Spleen, Am. J. M. Sc. **197**:90, 1939.

Dworacek and Pesta [510] were able to produce histologic changes in the spleen of an animal by intraperitoneal injection of kerasin. The serum kerasin was increased by this procedure.

A case of malignant Gaucher's disease is described by de Lange.[511] A child of the same parents had died of the same disease. The patient, an infant, aged 2½ months, showed neurologic symptoms (hypertonia, opisthotonos, convulsions, a positive Kernig sign) with splenomegaly, hepatomegaly, leukopenia, thrombopenia and fever. Death followed at the age of 5 months. Fifteen cases in 8 families have been reported.

In the diagnosis of Hand-Schüller-Christian disease Schüller [512] notes that roentgen evidence of hyperostotic osseous changes corresponding to the healing stage of xanthomatous processes in bone may be of diagnostic value. The bones involved may include the skull, pelvis and ribs. There may be roentgen evidence of miliary pulmonary nodules and visible changes in the skin and eyelids. The response to roentgen therapy is of importance in the diagnosis. Diseases which may cause a mistaken diagnosis are syphilis, tuberculosis, malignant disease, myeloma, osteitis fibrosa cystica, suppurative osteomyelitis, meningocoele spuria traumatica and circumscribed osteoporosis of the skull as seen with incipient Paget's disease.

Chargaff [513] isolated large amounts of sphingomyelin from the spleen of a patient with Niemann-Pick disease and obtained sphingosine, lignoceric acid and a mixture of palmitic and stearic acids on hydrolysis. Monoaminophosphatides containing 70 per cent cephalin were identified.

Lane and Smith [514] report 4 cases of Hand-Schüller-Christian disease with observations at autopsy. The cutaneous manifestations are emphasized.

BONE MARROW

With the popularization of the sternal puncture technic, there have been many references to quantitative data which are, in some cases, misleading. When material is drawn from the sternal marrow, it is

510. Dworacek, E., and Pesta, H.: Ueber einen spektralanalytischen Nachweis des Kerasins und experimentelle Cerebrosidspeicherung im Linne eines Morbus Gaucher, Wien. klin. Wchnschr. **52**:332, 1939.

511. de Lange, C.: Malignant Form of Gaucher's Disease, Acta pædiat. **27**: 34, 1939.

512. Schüller, A.: Diagnosis of Schüller-Christian's Disease, Brit. J. Radiol. **12**:225, 1939.

513. Chargaff, E.: The Spleen in a Case of Niemann-Pick's Disease, J. Biol. Chem. **130**:503-511, 1939.

514. Lane, C. W., and Smith, M. G.: Cutaneous Manifestations of Chronic (Idiopathic) Lipoidosis (Hand-Schüller-Christian's Disease): Report of Four Cases Including Autopsy Observations, Arch. Dermat. & Syph. **39**: 617-644 (April) 1939.

mixed with circulating blood, and all elements of the marrow are not washed out in equal proportion. Scott,[515] however, assumes that if only 0.1 cc. of material is withdrawn, it is pure marrow and is representative of all the marrow that remains in the sternal marrow cavity. He then reports differential counts of the cells to the first decimal place. In his "normals," myeloblasts vary 400 per cent. He does not take into account the fact that peripheral blood is mixed with the marrow and therefore finds 6.4 to 13.9 per cent of lymphocytes in normal marrow. Monocytes vary 300 per cent, basophilic normoblasts 283 per cent and myelocytes 700 per cent in different persons. Scott considers that authors using terminology that is different from his "abuse" the terms. He does not like the term "hemohistiocytes or blasts," so he does not find these cells present, forgetting that with his technic these cells may not be washed out. He finds no megaloblasts in normal bone marrow because he calls them pronormoblasts. He finds the technic useful in the diagnosis of myeloma, kala-azar and carcinoma.

Cotti [516] summarizes the criteria for the analysis of sternal puncture material as the total cell count, the relation between leukocyte and erythrocyte formation (normal, 3:1) and the per cent and quantitative relations between the stages of maturation and the number of cells undergoing mitosis.

Gordon [517] made quantitative studies of the cells of bone marrow by diluting them with acetic acid or with sodium citrate solution, and differential counts were made from films drawn from serum suspension of the cells. A somewhat similar method has been described by Isaacs.[518] In a normal person Gordon found the red blood cells to number 1,132,000 and the nucleated cells 468,000 per cubic millimeter of rib marrow. The red blood cell count was distinctly higher than this in cases of Addison's disease, stillbirth and some infections. There was an appreciable increase in the number of nucleated cells in infections, acute nephritis, Addison's disease and leukemia. The red blood cell count was lowest in cases of lymphatic leukemia and aplastic anemia; in 1 case of the latter it was 110,000 per cubic millimeter, with 28,000 nucleated cells. The bone marrow of the sternum, ribs and vertebra is essentially similar in man.

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515. Scott, R. B.: Sternal Puncture in the Diagnosis of Diseases of the Blood-Forming Organs, Quart. J. Med. **8**:127-172, 1939.

516. Cotti, L.: Kriterien zur anatomisch-funktionellen Beurteilung des Knochenmarks. Methodik und physiopathologische Anwendungen, Folia haemat. **62**:369, 1939.

517. Gordon, A. S.: Studies in Bone Marrow, J. Lab. & Clin. Med. **24**:352, 1939.

518. Isaacs, R.: Bone Marrow in Anemia: Red Blood Cells, Am. J. M. Sc. **193**:181, 1937.

Stasney and Higgins [519] observed a remarkable correlation in the percentage distribution of the various marrow elements in the flat bones of 14 persons after accidental death and suggested that data obtained from one region of the marrow will reveal trends in other portions of the marrow throughout the body. The myeloid-erythroid ratio is normally greater than 1 under physiologic conditions.

Kandel and LeRoy [520] point out that the great variation in the number and types of cells in normal marrow make it impossible to place great reliance on subtle changes in the constitution of material obtained by sternal puncture. In some cases such material does not give diagnostic data or is misleading in not expressing the true nature or extent of the disease. Clinical examination is often more valuable than inadequate data obtained by sternal puncture. Bone marrow in cases of pernicious anemia shows conversion from megaloblastic to normoblastic within twenty-four hours after liver therapy is given.

Williams [521] studied stained sections of bone marrow from various parts of the body from 288 persons representing 23 controls and also patients with many clinical conditions. Of those with presumably normal marrow, 39 per cent showed small lymphoid collections of cells. These appeared in a wide variety of diseases, often when no infection or significant inflammatory disease was demonstrable. They were found more frequently in persons over 40 years of age than in younger adults. The author concludes that no pathologic significance can be attached to these observations and that lymphoid nodules are essentially normal, though variable, constituents of active red bone marrow of adults.

Carbon injected into the bone marrow of dogs and titanium dioxide injected into that of rabbits in the experiments of Huggins [522] showed a symmetric distribution. In the red bone marrow pattern, centripetal regression, greater growth and retention at the rapidly growing metaphyses and formation of a central fatty cone in the long tubular bones were demonstrated. The foreign particles were held by the phagocytic cells of the marrow, showing the extent to which the marrow takes part in this process.

In cases of macrocytic anemia produced in rats by administration of sulfanilamide, Higgins and Machella [523] found an initial myeloid

519. Stasney, J., and Higgins, G. M.: A Cytologic Study of the Marrow in the Flat Bones of Man, Folia haemat. **61**:334, 1939.

520. Kandel, E. V., and LeRoy, G. V.: Limitations of Biopsy of Sternal Marrow, Arch. Int. Med. **64**:121 (July) 1939.

521. Williams, R. J.: The Lymphoid Nodules of Human Bone Marrow, Am. J. Path. **25**: 377, 1939.

522. Huggins, C.: A Quantitative Study of the Activity of the Reticuloendothelial Structures in Bone Marrow in Normal and Ischemic Limbs as Indicated by India Ink and Titamium Dioxide, Anat. Rec. **74**:231, 1939.

523. Higgins, G. M., and Machella, T. E.: The Bone Marrow of Rats Made Anemic by Administration of Sulfanilamide, Anat. Rec. **75**:529, 1939.

stimulation on the fourth day, but on the sixth day the per cent of erythroid cells exceeded that of the myeloid group in the marrow, accompanying the development of anemia in the peripheral blood. The myeloid-erythroid ratio, normally greater than 1, was always less than 1 from the sixth day on. There was no apparent eosinophilic stimulation in the marrow.

Nordenson [524] found two kinds of reticulum cells in human bone marrow. The first was a multipotent, primitive lymphoid reticulum cell, and the second, a phagocytic reticulum cell. Blood monocytes are derived from both types. The phagocytic reticulum cells stain intravitally and belong to the reticuloendothelial system. It is possible that the two types are identical but manifest different characteristics.

Stern [525] points out that besides the diagnostic value of studies of the bone marrow, the element of prognosis is important, as the normal, pathologic or aplastic nature of the marrow can be obtained.

In newborn children, Lichtenstein and Nordenson [526] found that the bone marrow did not differ markedly from that of the adult in regard to myelopoiesis and erythropoiesis. The latter is normoblastic; the "erythropoietic quotient" is 19 per cent (adults, 19 to 25 per cent). The authors describe the bone marrow of immature infants as "hyperplastic and youthfully immature in character." More immature cells appeared in the peripheral blood of such children than in that of normal infants. The "erythropoietic quotient" (for the peripheral blood) was 35 per cent during the first week of life and 32 per cent during the third. The maximum, 45 per cent, was noted at the age of 3 months, dropping to 24 per cent after eleven to fourteen months (i. e., more erythropoietic tissue, as compared with granulopoietic tissue, than normal). The marrow of premature infants is thus characterized as hyperplastic but insufficient, giving the paradoxic blood picture of hypoplastic anemia with leukopenia.

The sternal bone marrow in children was studied by Vogel and Bassen.[527] They punctured the thin manubrial well and sucked out marrow tissue. Total counts of nucleated cells varied from 50,000 to 1,000,000 per cubic millimeter, with an average of 300,000 to 400,000 for normal children. The ratio of myeloid to erythroid cells was

524. Nordenson, N. G.: Eine experimentelle Studie über die menschlichen Knochenmarkreticulumzellen sowie ein Beitrag zur Frage der Monozytengenese, Acta med. Scandinav. **100**:507, 1939.

525. Stern, L. D.: Bone Marrow from Clinical Diagnostic Viewpoint, J. Michigan M. Soc. **38**:38, 1939.

526. Lichtenstein, A., and Nordenson, N. G.: Studies on Bone Marrow in Premature Children, Folia haemat. **63**:155, 1939.

527. Vogel, P., and Bassen, F. A.: Sternal Marrow in Children in Normal and Pathologic States, Am. J. Dis. Child. **57**:245 (Feb.) 1939.

approximately 3 : 1. The changes in the bone marrow in pathologic conditions are described. Study of the bone marrow is of diagnostic value in cases of leukemia, infectious mononucleosis (elimination of leukemia), Gaucher's disease and Niemann-Pick disease. In other conditions, study of the marrow is helpful in eliminating other disease processes in making the diagnosis. (Excellent photomicrographs are presented.)

In children, Veeneklaas [528] found that the manubrium is the best site for sternal puncture. Megaloblasts 16 to 18 microns in diameter, similar to those found in the marrow of patients with pernicious anemia, are normal constituents but are present in small percentages. In children less than 3 years old megaloblasts, myeloblasts and "lymphoblasts" are more numerous than in older children. The marrow in the presence of pneumonia is characterized by an increase in myelocytes and plasma cells, and in cases of celiac disease large neutrophils (16 to 18 microns in diameter) appear. In the presence of aleukemic leukemia the leukemic cells in the marrow are of diagnostic importance even in the presence of a relatively normal peripheral blood picture.

Sternal puncture may be of great diagnostic help in cases of malaria, epecially when the organisms cannot be found in the blood, according to the report of Schretzenmayr and Lancaster.[529] When there is chronic malaria with splenomegaly and hepatic cirrhosis, a pernicious anemia–like blood picture may develop, justifying the use of liver extract. Sternal punctures are of value for the aplastic anemia associated with chronic ankylostomiasis. In cases of smallpox the authors found a myeloid reaction, with an increase in reticulum and plasma cells. Among the organisms which can be found in the sternal marrow are Leishman-Donovan bodies of kala-azar, as well as filaria and spirochetes. Sternal fluid may supplant blood transfusion when the latter is impracticable.

A considerable number of data have been accumulated by Osgood and Bracher [530] concerning the behavior of surviving marrow cells in vitro and their reaction to roentgen rays. There is a latent period of at least four days before polymorphonuclear neutrophils die, even after such large doses as 2,000 r. The theory that roentgen rays act only on cells in mitotic division appears improbable, as the number of cells affected at one time is far greater than the number undergoing mitotic division. As the probable duration of mitosis in these cells is in the neighborhood of twenty-four to one hundred hours, radium, which is

528. Veeneklaas, G. M. H.: Sternal Puncture in Children, Maandschr. v. kindergeneesk. **8**:45 and 118, 1938.

529. Schretzenmayr, A., and Lancaster, R. L.: Sternal Puncture with Special Reference to Its Application in Tropical Diseases in South China, J. Trop. Med. & Hyg. **41**: 341, 1938.

530. Osgood, E. E., and Bracher, G. J.: Culture of Human Marrow: Studies of the Effects of Roentgen-Rays, Ann. Int. Med. **13**:563, 1939.

applied for long periods, would be more likely to affect a "sensitive" stage than roentgen rays, which are applied for short periods. Some lymphocytes survive a dose of 2,000 r, while others disappear after a dose of 50 r. The authors observed no marked difference in the behavior of leukemic and nonleukemic cells. Osgood [531] found that cultures of marrow were helpful in evaluation of antibacterial therapeutic measures. In cell cultures inoculated with Staphylococcus aureus or alpha streptococci (Streptococcus viridans), neoarsphenamine in concentrations of 3 to 9 parts per million was far more effective than a 1 : 10,000 concentration of either sulfanilamide or sulfapyridine and did not damage the marrow cells significantly.

The influence of thyroid secretion on the bone marrow is noted in the marked myeloid metaplasia. Jones [146] finds that it resembles myelogenous leukemia. With recovery the marrow returns to normal. In cases of myxedema the marrow is markedly hypoplastic, improving with thyroid or thyroxine medication.

The bone marrow in cases of mycosis fungoides, as studied by Lapière and de Weerdt,[532] shows a histiocytoid reaction and inconstant eosinophilia. In the advanced stage of the disease there is an inhibition of the maturation of metamyelocytes into neutrophilic leukocytes, as well as a disturbance in the growth of the erythroblasts.

The myeloid tissue of the bone marrow in patients with gastric or duodenal ulcers was found by Bertolo and Ravetta [533] to be rich in cellular elements. When there were mild hemorrhages, the changes varied little from the normal. With severe hemorrhages there was an erythroblastic reaction, basophilic in the majority of cases. With moderate but persistent hemorrhage, basophilic and acidophilic erythroblasts were observed with signs of karyokinetic stimulation.

In the diagnosis of aplastic anemia, splenic anemia, Banti's disease, leukemia, metastatic neoplasm, Hodgkin's disease and thrombopenic purpura, Hardgrove and Van Hecke [534] find aspiration of the sternal marrow of value.

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531. Osgood, E. E.: Effectiveness of Neoarsphenamine, Sulfanilamide, Sulfapyridine in Marrow Cultures with Staphylococci and Alpha Streptococci, Proc. Soc. Exper. Biol. & Med. **42**:795, 1939; Marrow Cultures, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 219; The Culture of Human Marrow as an Aid in the Evaluation of Therapeutic Agents, J. Lab. & Clin. Med. **24**:954, 1939.

532. Lapière, S., and de Weerdt, W.: L'aspect de la moelle osseuse dans le mycosis fongoïde, Sang **13**:393, 1939.

533. Bertolo, A., and Ravetta, M.: Il tessuto mielode nelle ulcere gastriche e duodenali, Haematologica **20**:273, 1939.

534. Hardgrove, M., and Van Hecke, L. J.: Sternal Marrow Aspiration, Wisconsin M. J. **38**:111, 1939.

In 2 cases of carcinoma with metastases to the bone marrow Buchem and Hendriksen [535] concluded that the abnormalities in the blood depended on extramedullary hemopoiesis from either mechanical or toxic insufficiency of the bone marrow.

Poli [536] found that the plasma in the marrow has a higher protein content than that of the blood. The bone marrow is considered as a place of formation of plasma proteins.

Something of the nature of the fluid removed by sternal puncture is shown in the chemical analyses of Benda, Franchel, Ducatel and Nicolas.[537] In 25 normal persons the sugar in the marrow was equal to that in the blood or slightly less. In diabetic patients the level of marrow sugar was higher than that of blood sugar, but in other patients with hyperglycemia there was a wide variation. In 4 patients with anemia the marrow sugar was slightly greater (in per cent) than the blood sugar. The marrow iron in normal persons was slightly lower in amount than the blood iron (Benda, Poirot, and Franchel [538]). In 3 patients with anemia the iron in the marrow was from 8.9 to 9.4 per cent less than that in the blood, whereas in others the amount was equal to or greater than that in the blood, not depending on the number of red blood cells. In a case of bronze diabetes the level of iron in the marrow was 4.82 per cent higher than that in the blood, but after two months' treatment with insulin and ascorbic acid it was 5.09 to 6.07 per cent lower than that of the blood.

HEMATOLOGIC METHODS

Studies of the level of hemoglobin and other hematologic values for newborn children have been reported by Waugh and his associates.[539] Using the Evelyn photoelectric colorimeter, they found an average level of hemoglobin at birth of 15.6 Gm. per hundred cubic centimeters, with a decline of 0.66 Gm. during the first nine days. The average hematocrit value at birth was 51.3 per cent, with a fall of 5.4 per cent in the nine day period. During this time the mean corpuscular hemoglobin con-

535. Buchem, F. S. P., and Hendriksen, T. J. M.: Le syndrome sanguin en cas de tumeurs métastatiques de la moelle osseuse et de leucanémie, Acta med. Scandinav. **102**:243, 1939.

536. Poli, E.: Ricerche sull'emoproteinogenesi midollare, Sperimentale, Arch. di biol. **93**:455, 1939.

537. Benda, R.; Franchel, F.; Ducatel, J., and Nicolas, J.: Premiers résultats d'une étude sur le chemisme du suc médullaire prélevé par ponctions sternales: La glycomyélie, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:378, 1938.

538. Benda, R.; Poirot, G., and Franchel, F.: Recherches sur le fer médullaire, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:386, 1938.

539. Waugh, T. R.; Merchant, F. T., and Maughan, G. B.: Blood Studies on the Newborn: Determination of Hemoglobin, Volume of Packed Red Cells, Reticulocytes, and Fragility of the Erythrocytes over a Nine-Day Period, Am. J. M. Sc. **198**:646, 1939.

centration increased from 30 to 32 per cent. At birth the resistance to hypotonic solution of sodium chloride is the same as in the adult; during the first four days of life it increases, and subsequently it returns to normal.

The hemoglobin content of human blood was determined by Myers and Eddy [540] by the Newcomer acid hematin, the Hanzel iron and the Bing and Baker benzidine method. The average value for hemoglobin in men was found to be 15.8 Gm. and for women 13.0 Gm. per hundred cubic centimeters of blood. The authors concluded that calculation of hemoglobin from the iron content of the blood appears to be justifiable. A relation between hemoglobin concentration and body weight in men and rabbits was found by Spealman.[541] In men the hemoglobin content of the blood varies directly with the body weight, whereas in rabbits the relation is inverse. Hematologic standards for old men were formulated by Miller.[542] There were 160 subjects ranging in age from 60 to 104. The average erythrocyte count was 4,460,000 per cubic millimeter, with a range (including 95 per cent of the cases) between 3,500,000 and 5,500,000. The mean value for hemoglobin was 14.3 Gm. per hundred cubic centimeters, with a range of 12.0 to 17.5 Gm. The decrease in values associated with age was attributed to chronic low grade infections, nephrosclerosis and diminished cellularity of the bone marrow. Hypertension produced no demonstrable increase in the number of red cells. The leukocyte and differential counts apparently were not affected by advancing years. Standard normal values for erythrocytes, hemoglobin and packed cell volume throughout the last two trimesters of pregnancy were established by Bethell, Gardiner and MacKinnon.[190] The values for leukocytes and the sedimentation rates of young and older children and adolescents were studied by Osgood and his associates.[543]

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540. Myers, V. C., and Eddy, H. M.: The Hemoglobin Content of Human Blood, J. Lab. & Clin. Med. **24**:502, 1939.

541. Spealman, C. R.: Body Weight and Hemoglobin Concentration, Virginia M. Monthly **66**:591, 1939.

542. Miller, I.: Normal Hematologic Standards in the Aged, J. Lab. & Clin. Med. **24**:1172, 1939.

543. Osgood, E. E.; Baker, R. L.; Brownlee, I. E.; Osgood, M. W.; Ellis, D. M., and Cohen, W.: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Children Four to Seven Years of Age, Am. J. Dis. Child. **58**:61 (July) 1939; Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children Eight to Fourteen Years of Age, ibid. **58**:282 (Aug.) 1939; Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Adolescents Fifteen to Eighteen Years of Age, J. Lab. & Clin. Med. **24**:905, 1939. Osgood, E. E.; Brownlee, I. E.; Osgood, M. W., and Cohen, W.: Total Differential and Absolute Leukocyte Counts and Sedimentation Rates Determined for Healthy Persons Nineteen Years of Age and Over, Arch. Int. Med. **64**:105 (July) 1939.

Experimental studies on the effects of asphyxia were carried out by dei Poli and Cappellato.[544] Dogs, rabbits and cats were used, and asphyxia was produced by inhalation of carbon dioxide or illuminating gas. Rapid induction of asphyxia, within thirty to ninety seconds, caused no alteration in numbers of erythrocytes or platelets or in the coagulation time of the blood led to mild leukocytosis, which persisted for five to seven days. When asphyxia was produced more gradually, over a period of four to five minutes, a considerable increase occurred in the number of red cells, platelets and white cells both in the peripheral and in the central blood. The changes were prevented by removal of the spleen. Asphyxia produced over periods of ten to sixty minutes caused the same degree of changes in erythrocytes and leukocytes that occurred after the four to five minute period, but the increase in platelets was proportional to the degree of anoxemia. The increase in platelets was attributed both to contraction of the spleen and to new platelet formation, as evidenced by histologic examination of the hemopoietic organs. The coagulation time and the retraction of the clot were uninfluenced by asphyxia.

Delayed rates of platelet disintegration during menstruation and in persons with hemophilia were observed by Lee and Erickson.[545] These authors [265] also studied the platelets in normal persons and in subjects with hemorrhagic conditions. Olef's method of platelet enumeration was employed, and 400,000 to 600,000 per cubic millimeter were found in the blood of healthy men and nonmenstruating women. During menstruation there occurred a moderate decrease in the number of platelets. Intradermal injections of platelets caused a local reaction in normal persons, no reaction in hemophiliacs, a marked reaction in patients with idiopathic thrombopenic purpura, a negative result in persons with aplastic anemia and either a positive or a negative response in persons with various types of secondary purpura.

Direct enumeration and morphologic differentiation of platelets has been performed by Vilarino and Pimentel,[546] who used a solution containing an anticoagulant and a preservative. The solution is made up of 10 cc. of 3.8 per cent solution of sodium citrate, 10 cc. of solution of formaldehyde and 80 cc. of physiologic solution of sodium chloride. Equal parts of this fluid and venous blood are well mixed immediately

544. dei Poli, G., and Cappellato, M.: Sulle modificazioni prodotte dalla asfissia negli elementi morfologici e nel tempo di coagulazione del sangue; ricerche sperimentali, Haematologica **20**:505, 1939.

545. Lee, P., and Erickson, B. M.: Platelet Studies in Menstruation and Hemophilia: Total and Differential Counts, Disintegration Rates and Lipid Distributions, Proc. Soc. Exper. Biol. & Med. **39**:264, 1938.

546. Vilarino, and Vazquez Pimentel, J.: Ueber Thrombocytenzählungen, Klin. Wchnschr. **37**:1253, 1939.

after withdrawal. By this procedure the authors claim that change in the number and form of platelets can be prevented for as long as twenty-four hours, even at room temperature and without asepsis or paraffin coating of glassware.

Recently the Westergren method of measuring erythrocyte sedimentation has enjoyed increased popularity. Hambleton and Christianson [547] found that this procedure, with a tube 200 mm. long and an anticoagulant consisting of 15 to 20 per cent (by volume) of 3.8 per cent sodium citrate solution with a single reading at one hour gave results clinically more valuable than methods involving the use of heparin, correction for cell volume and graphic recording of results. Lamb [548] has emphasized the value of the sedimentation test to the general practitioner, and he considers correction for changes in red cell volume usually unnecessary. He recommends the use of the Westergren tube and a dry anticoagulant, ammonium oxalate 1.2 mg. and potassium oxalate 0.8 mg. for each cubic centimeter of blood, with readings at one hour. Studies in conjunction of the sedimentation rate and the nonfilament ratio were made by Stiles [549] in 292 cases of low grade chronic illness. The nonfilamented neutrophil ratio was expressed in percentage of the total neutrophils. The Westergren method was used without correction for anemia. All patients with symptoms of low grade chronic disease showed an increase in the nonfilament ratio, with a mean value of 25.2 per cent as compared to a normal average ratio of 6 per cent. More than 80 per cent of the patients exhibited an increase in the sedimentation rate, with an average fall of 15.9 mm. in one hour, as contrasted with 3 mm. and 5 mm., the normal limits for men and women, respectively. A direct relation was established between the results of both tests and increases in the severity of the illness. The nonfilament ratio appeared to reflect acute exacerbations, whereas the sedimentation rate was of greatest value in the diagnosis and follow-up of chronic illnesses.

A five hour sedimentation test was devised by Cutbill,[550] who used the Westergren tube. The degree of fall in each of the successive hours is expressed by means of an index. A new type of sedimentation tube

547. Hambleton, A., and Christianson, R. A.: The Choice of Technique for the Sedimentation Test, Am. J. M. Sc. **198**:177, 1939.

548. Lamb, F. H.: The Blood Sedimentation Test, J. Iowa M. Soc. **29**: 589, 1939.

549. Stiles, M. H.: Sedimentation Rate and Non-Filament Ratio in Low Grade Chronic Illness: A Statistical Analysis of Two Hundred and Ninety-Two Cases, Arch. Int. Med. **63**:664 (April) 1939.

550. Cutbill, L. J.: An Index of the Sedimentation Rate on a Mathematical Basis, Ann. Rheumat. Dis. **1**:359, 1939.

has been employed by Collins and his associates.[551] Dry potassium oxalate, 2 mg. per cubic centimeter of blood, is used as an anticoagulant; a 5 cc. graduated conical centrifuge tube is filled with blood, and the fall in red cells is read in one hour. Values are corrected to a packed cell volume of 42 per cent. The correction formulas are as follows: If the packed cell volume (P. C. V.) is less than 42 per cent, add $1.5 \times (42 - \text{P. C. V.})$ to the uncorrected reading; if P. C. V. is greater than 42 per cent, subtract $1 \times (\text{P. C. V.} - 42)$ from the uncorrected reading. The authors conclude that this method is the most accurate and informative of several tested. Brooks[552] described an instrument for measuring the sedimentation rate, which consists of a graduated pipet with a stopcock which may be attached directly to a needle used for venipuncture. The pipet is rinsed with an anticoagulant solution before being filled with blood to the 100 mm. mark. It is then disconnected from the needle and set upright. A photographic recording apparatus for the sedimentation rate has been devised by Nichols.[553]

Day[554] has pointed out that the reaction involved in the sedimentation of erythrocytes includes two incalculable phases: (1) rouleau formation at the beginning of the process and (2) packing effect at its conclusion. Consequently he advocates measuring only the maximum velocity of the fall rather than its total extent in a one hour period. However, the phase of rouleau formation, which the author wishes to disregard, is probably of considerable clinical significance. A recent review of the status of the sedimentation test has been published by Johnson.[555]

A method for the construction of hematocrit tubes from capillary glass tubing of uniform bore is described by Miller.[556]

Photoelectric optical methods for the study of blood coagulation have been reported by Lian and his associates,[557] and by Nygaard.[558] The

551. Collins, D. H.; Gibson, H. J.; Race, J., and Salt, H. B.: The Erythrocyte Sedimentation Test: A Wide-Bore Tube Method Using Oxalated Blood and Permitting Correction of the Result to a Standard Red Cell Volume, Ann. Rheumat. Dis. **1**:333, 1939.

552. Brooks, C.: New Technic for Blood Sedimentation Test, J. M. A. Alabama **9**:72, 1939.

553. Nichols, R. E.: A New Instrument for Automatically Recording the Erythrocyte Sedimentation Rate and the Volume Percentage of Cells and Plasma upon a Single Permanent Record, J. Lab. & Clin. Med. **24**:631, 1939.

554. Day, G.: The Behavior of Sedimenting Blood, Tubercle **20**:364, 1939.

555. Johnson, A. S.: The Present Status of the Blood Sedimentation Rate, New England J. Med. **220**:823, 1939.

556. Miller, A. T., Jr.: A Simple and Accurate Hematocrit Tube, J. Lab. & Clin. Med. **24**:547, 1939.

557. Lian, C.; Frumusan, P., and Sassier: Méthode optique por l'étude de la coagulation sanguine. Technique et résultats, Sang **13**:52, 1939.

558. Nygaard, K. K.: A New Apparatus for Photoelectric Recording of the Coagulability of Blood and Other Progressing Processes, J. Lab. & Clin. Med. **24**:517, 1939.

latter distinguishes for phases during the coagulation process, which may be recorded graphically in terms of changes of optical density of the plasma: (1) initial formation of fibrin, (2) period of gel formation, (3) rest period and (4) clot retraction period. Methods for the determination of the prothrombin content of the blood have been discussed elsewhere in this review.

The Weltmann serum coagulation reaction has been investigated by Levinson and Klein.[559] The test is said to distinguish between exudative and fibrotic processes. The reaction does not parallel the sedimentation rate but, according to the authors, seems to reflect more accurately the actual pathologic anatomic changes. The test is said to be especially valuable in the study of tuberculosis and rheumatic fever and in distinguishing septic from nonseptic febrile conditions.

559. Levinson, S. A., and Klein, R. I.: The Value of the Weltmann Serum Coagulation Reaction as a Laboratory Diagnostic Aid: Comparison with the Sedimentation Rate, Ann. Int. Med. **12**:1948, 1939.

REVIEW OF LITERATURE ON THE PITUITARY BODY (1938 AND 1939)

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This review, as was the last one on this subject,[1] is written by and for clinicians. Those who desire a more comprehensive review are referred to the second edition of Van Dyke's book, "The Physiology and Pharmacology of the Pituitary Body." [2] Other reviews have been published in the current literature.[3]

We have attempted to list our references under different headings, but overlapping has occurred. There have been errors of omission and commission in selecting these references, and not all of them are of equal importance. It is hoped, however, that the review is sufficiently complete to inform the reader as to current developments and trends in this young and fast changing field of endocrinology.

ROLE OF THE PITUITARY BODY IN CARBOHYDRATE METABOLISM

It is exceedingly difficult to separate the discussion of the metabolism of any single food constituent from that of the metabolism of other food constituents. It is equally difficult to interpret any phase of metabolism in terms of any single gland. The relation of the pituitary body to the metabolism of carbohydrate foods is therefore complex.

From the Division of Medicine, the Mayo Clinic.

1. Rynearson, E. H., and Hodgson, C. H.: Recent Advances in Knowledge of the Anterior Lobe of the Hypophysis, Arch. Int. Med. **62**:160-176 (July) 1938.

2. Van Dyke, H. B.: The Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1938, vol. 2.

3. Collip, J. B.: Results of Recent Studies on Anterior Pituitary Hormone, Edinburgh M. J. **45**:782-804 (Nov.) 1938. Evans, H. M.: Endocrine Glands: Gonads, Pituitary, and Adrenals, Ann. Rev. Physiol. **1**:577-652, 1939. Jensen, H., and Tolksdorf, S.: The Relation of the Anterior Pituitary to Sex and Metabolism, Endocrinology **25**:429-436 (Sept.) 1939. Sexton, D. L.: Experiences with Pituitary Hormone Therapy, Tr. Am. Therap. Soc. **38**:89-95, 1938.

A complete review of this subject was written by Jane Russell.[4] Because of its importance, we wish to quote her summary in its entirety.

The complex relationship of the anterior pituitary to carbohydrate metabolism has only just begun to be explored. Some facts have been established definitely, and the discussions in this paper concerning the most important of these may be summarized as follows:

1. Hypophysectomized animals are remarkably hypersensitive to insulin and may show diminished responses to epinephrine. Although several theories have been advanced to explain these abnormalities, none is sufficiently supported by present evidence to be accepted as final.

2. The removal of the hypophysis alters markedly the response of the animal to pancreatectomy, apparently ameliorating the effects of this operation. Possible mechanisms for this action have been discussed.

3. Anterior lobe extracts may affect the carbohydrate metabolism of normal, depancreatized or depancreatized-hypophysectomized animals in a manner which is outwardly "contra-insular" or "diabetogenic." This action cannot be considered simply in this light, however, for not all of the effects are similar to those of pancreatectomy, and the mechanism of their action is unknown.

Other types of action of anterior lobe extracts on the carbohydrate metabolism of normal animals are not at present well enough established to be given a definite place in anterior pituitary physiology.

4. Hypophysectomized animals when in good condition and well fed exhibit no marked abnormalities in their carbohydrate metabolism except those noted above; but they suffer an impairment in the normal mechanism by which blood sugar levels are maintained and, apparently, by which the tissue carbohydrate reserves are preserved, in conditions in which the carbohydrate supply is interrupted (as in fasting, phlorhizin poisoning, etc.).

In the rat, the abnormal rate of depletion of carbohydrate reserves during fasting is accompanied by an apparent increase in the rate of carbohydrate oxidation. Both of these effects can be prevented by anterior lobe therapy.

Two principal theories have been advanced in explanation of these and related findings—one, that the anterior lobe controls gluconeogenesis from endogenous protein, if not from fat, administration of its extract causing an increase in available glucose and its removal curtailing the supply; the other theory, that the anterior lobe influences carbohydrate oxidation itself, its presence preventing carbohydrate loss below certain levels and its absence characterized by lack of restraint on carbohydrate oxidation under conditions when such would ordinarily occur. Although this reviewer inclines to the latter explanation, at present it is not possible to make a final decision as to the validity or completeness of either of these theories.

Many observers were deeply impressed with the close and important relation between the anterior lobe of the pituitary body and carbohydrate metabolism [5] but said they did not believe that a pituitary hormone would produce permanent diabetes mellitus. The first evidence of such

4. Russell, J. A.: The Relation of the Anterior Pituitary to Carbohydrate Metabolism, Physiol. Rev. **18**:1-27 (Jan.) 1938.

5. Long, C. N. H.: The Relation of Anterior Pituitary to Carbohydrate Metabolism, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:276-286, 1938.

an effect was reported by Young [6] in two papers published in March 1938. He used a crude anterior pituitary extract obtained from oxen on mice, rats, guinea pigs, rabbits, cats and dogs. The mice, rats and guinea pigs appeared to be almost totally insensitive to the diabetogenic action of this extract; in the case of rabbits and cats, glycosuria and ketonuria followed the daily injection of crude extract in 25 to 50 per cent of cases, but with dogs he had only 1 failure in 25 experiments. Young reported that in the dog glycosuria, hyperglycemia and ketonuria appeared after three or four injections and then disappeared and reappeared when an increased dose was given. When sufficient amounts were administered, the diabetic condition was found to continue indefinitely after cessation of the injections. This extract caused no immediate marked increase in the blood sugar, but required three or four daily injections.

Young was wise in emphasizing that the principle concerned should be called "diabetogenic factor" (rather than a "diabetogenic hormone"), and he suggested that this name be reserved for the substance or substances in an anterior pituitary extract which possess diabetogenic activity and which have little or no effect on blood sugar values within a few hours after the injection. The diabetogenic effect, he said, is contained in neither prolactin [7] nor the glycotropic (anti-insulin) factor [8] with which it is closely associated, but is a distinct substance, since the administration of prolactin or of the glycotropic (anti-insulin) factor does not induce a diabetic condition but produces, rather, transient glycosuria, unaccompanied by polyuria and ketonuria. This "hormone" has been further studied by Himsworth and Scott.[9]

This important work was repeated by Campbell and Best,[10] who injected an extract into a normal dog for seventeen days, with the production of a gradually increasing diabetogenic response. On the

6. Young, F. G.: The Diabetogenic Action of Crude Anterior Pituitary Extracts, Biochem. J. **32**:513-523 (March) 1938; Studies on the Fractionation of Diabetogenic Extracts of Anterior Pituitary Gland, ibid. **32**:524-533 (March) 1938.

7. Anderson, C. M.: Pituitary Gland and Carbohydrate Metabolism: Influence of Prolactin on Carbohydrate Metabolism, M. J. Australia **1**:701-704 (April 16) 1938.

8. Newton, W. H., and Young, F. G.: The Influence of the Glycotropic (Anti-Insulin) Factor of the Anterior Hypophysis on the Insulin Sensitivity of the Hypophysectomized Rabbit, J. Physiol. **94**:40-46 (Oct. 14) 1938.

9. Himsworth, H. P., and Scott, D. B. M.: The Action of Young's Glycotropic Factor of the Anterior Pituitary Gland, J. Physiol. **92**:183-207 (March 14) 1938.

10. Campbell, J., and Best, C. H.: Production of Diabetes in Dogs by Anterior-Pituitary Extracts, Lancet **1**:1444-1445 (June 25) 1938.

seventeenth day the dog excreted 126 Gm. of sugar, and after the injections of the extract were stopped excretion of dextrose continued in even greater quantities than before. It is interesting to note that the diabetes responded promptly to treatment with insulin. On the fifty-eighth day total pancreatectomy was performed and produced but slight effect on the requirement of insulin. The dog was later killed, and a section of the pancreas showed that an extreme degree of hydropic degeneration of the islet cells was present, with particularly extensive changes in the beta cells. An assay of the pancreas revealed a marked decrease in its content of insulin.

Dohan and Lukens [11] and Loubatières [12] also have corroborated the aforementioned finding. An effort has been made by Bergman and Turner [13] to assay the diabetogenic hormone, but it is doubtful whether they were using the same hormone, since their test was dependent on a prompt response rather than on the more delayed and more permanent response reported by the other workers.

It is, of course, impossible to know how much of the effect of this and similar hormones is referable to direct action on the pancreas. Santo [14] was not able to demonstrate any pancreatropic effect by means of histologic study of the pancreas of animals into which the pancreatropic hormone had been injected. However, the hormone may not have been effective, since Richardson and Young [15] reported definite changes as occurring in the islet cells after the injection of a pancreatropic extract. Their method of study was unique in that they projected microscopic fields on sheets of cartridge paper. They then "cut out" different regions and weighed the islet and acinar regions separately. In this study they again found the peculiar differences which occur in species, for they observed a far different islet-acinar ratio in the Wistar strain of rats than in another strain. The extract which increased the islet-acinar ratio had little or no effect on the blood sugar of the rats studied.

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11. Dohan, F. C., and Lukens, F. D. W.: Persistent Diabetes Following the Injection of Anterior Pituitary Extract, Am. J. Physiol. **125**:188-195 (Jan.) 1939.

12. Loubatières, A.: Recherches sur le diabète sucré permanent consécutif aux injections d'extrait de lobe antérieur d'hypophyse chez le chien normal, Compt. rend. Acad. d. sc. **208**:1933-1935 (June 12) 1939.

13. Bergman, A. J., and Turner, C. W.: The Biological Assay of the Carbohydrate Metabolism Hormone of the Anterior Pituitary, J. Biol. Chem. **123**:471-477 (April) 1938.

14. Santo, E.: Die Beeinflussung der Langerhansschen Inseln durch das sog. pankreatrope Hormon der Hypophyse, Ztschr. f. d. ges. exper. Med. **102**:390-406, 1938.

15. Richardson, K. C., and Young, F. G.: The "Pancreotropic" Action of Anterior Pituitary Extracts, J. Physiol. **91**:352-364 (Dec. 14) 1937.

In a second paper Richardson and Young [16] reported on a study of the pancreas of dogs which had been rendered diabetic for at least ten months after the injections had been stopped; they observed marked changes in the islet cells, particularly hydropic degeneration and depletion of the cytoplasmic granules in the beta cells. There was some proliferation of the islet cells, a change which they said may precede exhaustive or degenerative processes that accompany the onset of permanent diabetes. They compared their results with those reported by Allan (1922), who found that, according to observations on his animals, the onset of diabetes is accompanied by functional exhaustion of the beta cells; then cytoplasmic granules are lost and the beta cells hypertrophy; next, vacuolation and disappearance of the cells occur after degeneration of nuclei.

The important relation of the adrenal cortex to carbohydrate metabolism is receiving much attention. Russell [17] expressed the belief that there is a complementary and synergistic relation between the metabolic activities of the adrenal cortical hormone and those of the anterior pituitary hormones. Corey and Britton [18] have restated their concepts, emphasizing the intimate relation between the pituitary and adrenal glands in carbohydrate metabolism. They concluded that the inability of hypophysectomized animals to maintain normal values for carbohydrates for short periods is explainable on the basis of adrenocortical deficiency, and they noted that the administration of adrenal cortical extract has been shown to be effective in maintaining normal and supernormal values for blood sugar and liver glycogen in hypophysectomized rats. Glycogen in the muscle likewise may be kept at approximately normal values. This extract will also restore the values for blood sugar and liver glycogen to normal levels in hypophysectomized rats which have been subjected to a twelve hour fast before the beginning of injections.

Bennett [19] reviewed the evidence supporting the concept that the pituitary body directly influences the maintenance of fasting carbohydrate values in the rat rather than that this maintenance is achieved through the mediation of the adrenal gland. Hypophysectomized rats

16. Richardson, K. C., and Young, F. G.: Histology of Diabetes Induced in Dogs by Injection of Anterior-Pituitary Extracts, Lancet **1**:1098-1101 (May 14) 1938.

17. Russell, J. A.: Effects of Anterior Pituitary and Adrenal Cortical Extracts on Metabolism of Adrenalectomized Rats Fed Glucose, Proc. Soc. Exper. Biol. & Med. **41**:626-628 (June) 1939.

18. Corey, E. L., and Britton, S. W.: Hypophyseal and Adrenal Interrelationships and Carbohydrate Metabolism, Am. J. Physiol. **126**:148-154 (May) 1939.

19. Bennett, L. L.: The Interrelation of Pituitary and Adrenal in the Control of Carbohydrate Levels in the Rat, Endocrinology **22**:193-196 (Feb.) 1938.

immediately after operation become unable to maintain fasting values for glycogen in the muscle, whereas this defect does not develop in adrenalectomized rats for several hours after operation. The fasting value for glycogen in the muscle of adrenalectomized rats is maintained within normal limits by treatment with adrenal cortical extract and salt; this treatment is without effect on hypophysectomized rats. Crude anterior pituitary extracts maintain the fasting glycogen value of hypophysectomized rats in the absence of both adrenal glands. Bennett stated the opinion that this factor, acting independently of the adrenal glands, has not been identified with any of the known hormones of the anterior lobe of the pituitary body.

Lukens and Dohan [20] found adrenal cortical extract capable of compensating to a considerable extent for the diabetes of adrenalectomized and depancreatized animals. Long and Katzin [21] were able, by using an adrenal cortical extract (or Kendall's crystalline compound), to prevent the depletion of carbohydrate stores in fasting, hypophysectomized rats, and they succeeded in restoring the values for blood sugar, liver and muscle glycogen, even though these values first had been lowered by fasting. Long and Katzin did not attempt to define the mechanism of this effect, but suggested as its basis either a decreased utilization of carbohydrate or an increased production of dextrose from noncarbohydrate sources. Reiss and his associates [22] treated hypophysectomized rats with corticotropic hormone and found that the therapy increased the ability of the animals to store sugar and fat.

Soskin and his co-workers [23] studied the relation of thyroxin to carbohydrate disturbances following hypophysectomy and found that administration of thyroxin would maintain a normal value for blood sugar through long periods of fasting. Thyroxin did not diminish sensitivity to insulin in the dogs in this series. This relation of sensitivity to insulin has been studied by Brobeck and associates,[24] who found that responses

20. Lukens, F. D. W., and Dohan, F. C.: Further Observations on the Relation of the Adrenal Cortex to Experimental Diabetes, Endocrinology **22**:51-58 (Jan.) 1938.

21. Long, C. N. H., and Katzin, B.: Effect of Adrenal Cortical Hormone on Carbohydrate Stores of Fasted Hypophysectomized Rats, Proc. Soc. Exper. Biol. & Med. **38**:516-518 (May) 1938.

22. Reiss, M.; Kusakabe, S., and Budlowsky, J.: Zur Beziehung zwischen Hypophysenvorderlappen und Kohlehydratstoffwechsel, Ztschr. f. d. ges. exper. Med. **104**:55-70, 1938.

23. Soskin, S.; Levine, R., and Heller, R. E.: Rôle of the Thyroid in the Carbohydrate Disturbance Which Follows Hypophysectomy, Am. J. Physiol. **125**:220-226 (Feb.) 1939.

24. Brobeck, J. R.; Magoun, H. W., and Ranson, S. W.: Insulin Sensitivity of Monkeys After Section of the Hypophyseal Stalk, Proc. Soc. Exper. Biol. & Med. **42**:622-624 (Nov.) 1939.

to insulin may be entirely normal when only a half of the anterior lobe of the pituitary body is left intact. The presence of infundibular connections between the hypophysis and the pars distalis, however, is not essential for maintenance of normal sensitivity to insulin in the monkey and is probably not essential for maintenance of normal carbohydrate metabolism.

The important relation of the liver to carbohydrate metabolism has been studied by many investigators. Franseen, Brues and Richards [25] studied the effect of hypophysectomy on the restoration of the liver following partial hepatectomy in rats and found that restoration took place at a somewhat lower rate than in normal rats maintained on an optimal diet but at a more rapid rate than in fasting rats.

Soskin and his associates [26] found that hypophysectomized dogs utilized carbohydrate only about half as effectively as normal dogs. They concluded that the effects of hypophysectomy cannot be referable to an increased rate of utilization of sugar, since that rate is actually diminished. They wrote that hypoglycemia and other evidences of carbohydrate disturbance must be attributed to a proportionately greater decrease in the rate of new formation of sugar by the liver. Russell [27] has continued her studies in this field and has reported on a factor of the anterior lobe of the pituitary body which maintains glycogen in the muscles in fasting hypophysectomized rats, a factor which she said is not associated with the effect of many of the established hormones of the anterior lobe of the pituitary body. In a later article, Russell [28] concluded that the anterior lobe of the pituitary body is concerned not only with the preservation of carbohydrate values during the period of fast but also with the disposition of carbohydrate when the animal is fed. In the hypophysectomized rat the proportion of absorbed dextrose oxidized and the proportion of total calories obtained from carbohydrate sources were both much higher than in normal animals. Injection of an extract of the anterior lobe of the pituitary body into hypophysectomized and into normal rats caused an immediate decrease in the apparent rate of oxidation after feeding with carbohydrates.

25. Franseen, C. C.; Brues, A. M., and Richards, R. L.: The Effect of Hypophysectomy on the Restoration of the Liver Following Partial Hepatectomy in Rats, Endocrinology **23**:292-301 (Sept.) 1938.

26. Soskin, S.; Levine, R., and Heller, R. E.: Carbohydrate Utilization in the Hypophysectomized Dog, Proc. Soc. Exper. Biol. & Med. **38**:6-8 (Feb.) 1938. Soskin, S.; Levine, R., and Lehmann, W.: Influence of the Hypophysis on Carbohydrate Metabolism, Am. J. Physiol. **127**:463-469 (Oct.) 1939.

27. Russell, J. A.: The Anterior Pituitary Factor Which Maintains Muscle Glycogen in Fasted Hypophysectomized Rats, Endocrinology **22**:80-85 (Jan.) 1938.

28. Russell, J. A.: The Effects of Hypophysectomy and of Anterior Pituitary Extracts on the Disposition of Fed Carbohydrate in Rats, Am. J. Physiol. **121**: 755-764 (March) 1938.

Anderson,[29] Marks and Young [30] and Young [31] also discussed the separate identity of this principle.

Efforts to determine whether diabetogenic hormones are excreted in the urine continue. Clay and Lawson [32] found that in the urine of 19 of 22 pancreatectomized dogs, a substance consistently appeared which had significant power to raise the values for sugar in the blood. Using rabbits as test animals, Clay and Lawson confirmed the presence in the urine of human beings with diabetes of a blood sugar–raising principle which is not found in the urine of normal persons. Administration of insulin and raw pancreas tissue did not cause disappearance of this principle from the urine of the depancreatized dogs. If, however, the dogs had been previously hypophysectomized, pancreatectomy did not cause the appearance of this substance in the urine. Hypophysectomy caused the principle to disappear from the urine of depancreatized dogs. Bjering [33] studied the urine of healthy, of diabetic and of pregnant nondiabetic patients. He found in the urine obtained from healthy subjects, small quantities of a factor which had the power of elevating the values for blood sugar; in the urine obtained from some of the diabetic patients, an absolute increase of this principle, and in that of pregnant nondiabetic patients, large quantities of this principle. The urine of some of the diabetic patients did not contain an excessive amount of the principle. Lucke and his associates [34] studied the excretion of the contrainsular hormone and observed that the cerebrospinal fluid obtained from animals which were rendered markedly hypoglycemic had a hyperglycemic effect when injected into normal animals.

Clinical Aspects.—Friedman [35] reported 2 cases in which the patients had hyperinsulinism and were found to have both the typical adenomas

29. Anderson, C. M.: Anterior Pituitary Gland and Carbohydrate Metabolism, M. J. Australia **1**:11-19 (Jan. 1) 1938.

30. Marks, H. P., and Young, F. G.: The Influence of Anterior Pituitary Extracts Injected Either With or Without Insulin, on the Glycogen Contained in the Livers of Fasting Young Rabbits, J. Physiol. **93**:61-73 (June 14) 1938.

31. Young, F. G.: The Identity and Mechanism of Action of Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, Biochem. J. **32**:1521-1539 (Sept.) 1938.

32. Clay, H. L., and Lawson, H.: Relationship of Hyperglycemic Principle in Diabetic Urine to Pancreas and Hypophysis, Am. J. Physiol. **125**:566-570 (March) 1939.

33. Bjering, T.: Investigation of the Diabetogenous Hormone in Urine: Preliminary Report, Acta med. Scandinav. **94**:483-496, 1938.

34. Lucke, H., and Werner, R.: Untersuchungen über die Ausschüttungsbedingungen des kontrainsulären Hormons aus dem Hypophysenvorderlappen, Ztschr. f. d. ges. exper. Med. **102**:242-247, 1938. Lucke, H., and Koch, A.: Die reaktive Ausschüttung des kontrainsulären Vorderlappenhormons bei der Phlorrhizinglykosurie, ibid. **103**:270-273, 1938.

35. Friedman, N. B.: Chronic Hypoglycemia: Report of Two Cases with Islet Adenoma and Changes in the Hypophysis, Arch. Path. **27**:994-1010 (June) 1939.

of the islets of Langerhans and changes in the basophilic and eosinophilic cells of the pituitary body.

Shepardson and Shapiro [36] reviewed the subject of diabetes among bearded women and found only 17 clearcut cases of the condition, to which they added another case. Because of the rarity of true diabetes in the presence of disturbances of the adrenal cortex, they suggested that in those patients afflicted by the Achard-Thiers syndrome the precursor of diabetes must be present.

Bartelheimer [37] suggested the possibility that two types of diabetes might exist: one associated with underfunction of the islands of Langerhans and the other caused by hyperfunction of the anterior lobe of the pituitary body and the adrenal cortex.

Lassen and Hanson [38] injected an alkaline extract of the pituitary body into 3 patients with diabetes and obtained a diabetogenic effect.

Elmer and associates [39] found no evidence of a pancreatropic "blood sugar–decreasing" hormone and said that the anterior lobe of the pituitary body secreted only a blood sugar–raising substance, which they found in the blood of patients suffering from acromegaly.

Gessler and associates [40] studied the effect of injection of estrogenic substances on the blood sugar of female diabetic patients after the menopause. Among a small series of patients, they found a significant decrease in the value for fasting blood sugar in 2 patients in whom the onset of diabetes mellitus coincided with that of the menopause and also a decrease in this value in a patient in whom the menopause preceded the onset of diabetes mellitus. In 2 other patients no effect resulted from the injections of this estrogenic substance. Gessler and associates said that the beneficial effect was referable to inhibition of the pituitary diabetogenic factor by the estrogen.

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36. Shepardson, H. C., and Shapiro, E.: The Diabetes of Bearded Women (Suprarenal Tumor, Diabetes, and Hirsutism): A Clinical Correlation of the Function of the Suprarenal Cortex in Carbohydrate Metabolism, Endocrinology **24**:237-252 (Feb.) 1939.

37. Bartelheimer, H.: Hypophysärer Diabetes, Deutsches Arch. f. klin. Med. **184**:185-199, 1939.

38. Lassen, H. C. A., and Hanson, L.: Investigations into the Effect of the Anterior Pituitary Extract on the Carbohydrate Metabolism in Normals and in Diabetics, Acta med. Scandinav., 1938, supp. 89, pp. 288-299.

39. Elmer, A. W.; Giedosz, B., and Scheps, M.: The Anterior Pituitary and Its Diabetogenic and Pancreatotropic (Blood-Sugar Decreasing) Activity, Acta med. Scandinav. **93**:487-498, 1937.

40. Gessler, C. J.; Halsted, J. A., and Stetson, R. P.: Effect of Estrogenic Substance on Blood Sugar of Female Diabetics After Menopause, J. Clin. Investigation **18**:715-722 (Nov.) 1939.

Culpepper and co-workers [41] have continued Hutton's observations on the treatment of diabetes mellitus by irradiation of the pituitary and the adrenal region, with inconclusive results.

Johnson and associates [42] used tremendous doses of roentgen therapy in the treatment of experimentally induced diabetes in dogs. The doses far exceeded that which it is possible to employ for human beings and had no effect on the diabetes.

Bartelheimer [43] wrote that attempts to treat diabetes with pituitary hormone have not yet arrived at a point at which such therapy is satisfactory for clinical application. In several instances he has succeeded in decreasing the value for blood sugar and has caused a decrease in the sugar content of the urine following the administration of androgens and estrogens.

Summary.—We introduced this discussion with a complete summary of Russell's review. We shall close with a briefer summary of two excellent discussions by Young.[44] That author discussed the evidence at hand which would suggest that the anterior lobe of the pituitary body has several separate but related effects on carbohydrate metabolism. These are: (1) an anti-insulin or glycotropic effect, which diminishes sensitivity to insulin; (2) an effect (glycostatic) on the storage of glycogen, a result closely comparable to that produced by the hormones of the adrenal cortex; (3) an effect (pancreatropic) on the islands of Langerhans, causing an increase in the number and size of the cells; (4) a diabetogenic effect, the fraction producing this result being the one which can induce permanent diabetes mellitus, and (5) a ketogenic effect (Shipley and Long [45] have suggested that the ketogenic, the growth and the diabetogenic factor all may be identical).

Finally, we recommend the reading of a symposium on carbohydrate metabolism which was published in *Endocrinology*.[46] This symposium

41. Culpepper, W. L.; Madden, E. E.; Olson, E. C., and Hutton, J. H.: Treatment of Essential Hypertension and Diabetes Mellitus by Irradiation of the Pituitary and Adrenal Regions, Endocrinology **22**:236-242 (Feb.) 1938.

42. Johnson, J. B.; Selle, W. A., and Westra, J. J.: Massive Roentgen Irradiation of the Hypophysis in Experimental Diabetes, Am. J. Roentgenol. **39**:95-102 (Jan.) 1938.

43. Bartelheimer, H.: Hypophysenvorderlappen und Diabetes, Klin. Wchnschr. **18**:647-651 (May 6) 1939.

44. Young, F. G.: The Relation of the Anterior Pituitary Gland to Carbohydrate Metabolism, Brit. M. J. **2**:393-396 (Aug. 19) 1939; The Pituitary Gland and Carbohydrate Metabolism, Endocrinology **26**:345-351 (Feb.) 1940.

45. Shipley, R. A., and Long, C. N. H.: Studies on the Ketogenic Activity of the Anterior Pituitary: I. The Relation of Ketonaemia to Ketonuria in the Rat; II. A Method for the Assay of the Ketogenic Activity; III. The Nature of the Ketogenic Principle, Biochem. J. **32**:2242-2256 (Dec.) 1938.

46. Cori, C. F.: Glycogen Breakdown and Synthesis in Animal Tissues, Endocrinology **26**:285-296 (Feb.) 1940.

includes a discussion of the relation of all the glands of internal secretion to carbohydrate metabolism.

ROLE OF THE PITUITARY BODY IN PROTEIN AND FAT METABOLISM

Studies on the relation of the anterior lobe of the pituitary body to metabolism have been extensive. The usual difficulties in interpreting these results have been encountered because of the marked variation which occurs with different species, nutritional circumstances, the time of year the study was made, the type of hormones injected and other factors. Phillips and Robb [47] have confirmed Cori's observations concerning the delayed intestinal absorption of dextrose in the hypophysectomized rat. This fact should be kept in mind in interpreting studies of metabolism which involve feeding by mouth. Mirsky [48] has reported a study of the relation of the anterior lobe of the pituitary body to protein metabolism following the administration of a crude alkaline extract. He observed a decreased rate of protein breakdown of normal dogs and an increase in the rate of protein catabolism in depancreatized dogs. The suggestion is made that the anterior lobe of the pituitary body exerts a direct effect on muscle, an effect which is in opposition to that observed in the intact animal. It is postulated that the synthesis of muscle protein consequent to the administration of extracts of the anterior lobe of the pituitary body may be dependent on the simultaneous stimulation of the pancreas. Goldzieher [49] studied the relation of the anterior lobe of the pituitary body to the specific dynamic action of protein. After the intake of a large protein meal the specific dynamic action of protein is present but is lower in hypophysectomized animals (Houssay). Goldzieher commented on the fact that in clinical examples of "hyperpituitarism" (by which term he referred to menopausal and castration states) there is evidence of a "high normal and increased dynamic action." He noted an increase in specific dynamic action in obese diabetic patients and absence of specific dynamic action in the presence of acute infections, but he found no evidence that the function of the thyroid gland has any influence on production of heat subsequent to stimulation with protein. He concluded that the thyrotropic hormone cannot be the means by which the pituitary body affects the specific dynamic action. An increase in the production of heat after the ingestion of protein occurs

47. Phillips, R. A., and Robb, P. D.: Metabolism Studies in the Albino Rat: Carbohydrate Studies After Hypophysectomy, Endocrinology **25**:187-192 (Aug.) 1939.

48. Mirsky, I. A.: The Influence of the Anterior Pituitary Gland on Protein Metabolism, Endocrinology **25**:52-56 (July) 1939.

49. Goldzieher, M. A.: Relation of the Anterior Lobe to the Specific Dynamic Action of Protein. A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:536-546, 1938.

largely in the liver and is only indirectly influenced by a deficiency or an excess of hormone of the anterior lobe of the pituitary body.

The influence of anterior pituitary extract on the proteins of the liver has been studied by Houchin.[50] He found that the injection of pituitary extracts did not cause true hypertrophy of the entire liver. The percentage of water did not vary significantly in the treated subjects as compared with similar percentages in untreated controls. The alkali-soluble protein of the liver was decreased by a principle present in the anterior lobe of the pituitary body. This decrease of the protein fraction was between 35 and 53 per cent of the normal. An increase was observed in the protein fraction containing insoluble proteins and proteins that originally were soluble in water or dilute salts; also noted was an increase in soluble nonprotein materials. This hormone, Houchin stated, is entirely separate from any of the other metabolic hormones of the pituitary body, and he termed it a "protein metabolism hormone."

Schrire and Sharpey-Schafer [51] found that the administration of thyrotropic extract increases the elimination of urinary creatine by stimulating the thyroid gland to increased activity. The excretion of creatinine is unaffected. Gonadotropic extract increases the excretion of creatinine without affecting creatine. Gonadotropic substances from urine and from blood serum have no effect. The factor influencing the elimination of creatinine appears to be inseparable from the pituitary gonadotropic principle. Pizzolato and Beard [52] injected various hormonal preparations into normal and into castrated rats and studied the effect of these injections on creatine-creatinine metabolism. They suggested a possible synergistic action of the hormones in the body on creatin-creatinine metabolism. Koven and Beard [53] also reported the effect of the injection of sex hormones on creatine and creatinine metabolism.

Cope and his associates [54] studied the relation of the pituitary body to amylase activity. In a dog with intact anterior pituitary tissue and permanent diabetes insipidus resulting from ablation of the posterior lobe of the pituitary body and stalk, there was no change in amylase activity in the blood serum. Loss of the posterior lobe was therefore excluded

50. Houchin, O. B.: The Influence of Anterior Pituitary Extracts on the Proteins of the Liver, Endocrinology **25**:759-767 (Nov.) 1939.

51. Schrire, I., and Sharpey-Schafer, E. P.: Observations on Pituitary Control of Creatine and Creatinine Excretion, Clin. Sc. **3**:369-376 (Dec.) 1938.

52. Pizzolato, P., and Beard, H. H.: Creatine-Creatinine Metabolism and the Hormones, Endocrinology **24**:358-363 (March) 1939.

53. Koven, A. L., and Beard, H. H.: Creatine-Creatinine Metabolism and the Hormones: II. Progestin and Antuitrin-T, Endocrinology **25**:221-226 (Aug.) 1939.

54. Cope, O.; Kapnick, I.; Lambert, A.; Pratt, T. D., and Verlot, M. G.: Endocrine Function and Amylase Activity: III. Further Observations of Blood Serum Amylase Activity in Relation to Pituitary, Pancreas and Thyroid Function in the Dog and Rabbit, Endocrinology **25**:248-256 (Aug.) 1939.

as the source of the increase in amylase activity previously described as following total hypophysectomy. According to the observations of those investigators, injection of extract of the anterior lobe of the pituitary body into the normal dog causes a decrease in amylase activity in the blood serum. The decrease in amylase activity in acidosis following pancreatectomy in the dog and the increase to normal after the administration of insulin are confirmed. In the pancreatectomized hypophysectomized dog, amylase activity remains within normal limits. The absence of effect of insulin on amylase activity in the serum of the normal animal is not confirmed. Insulin hypoglycemia, maintained for more than six hours, results in a decrease in activity in dogs and rabbits. If hypoglycemia is maintained in the dog, the value reached in thirty-six hours is comparable to that seen in the presence of diabetic acidosis. Thyroidectomy and the administration of thyroxin produce in the dog and rabbit only a greater variation of activity of the serum amylase system. No consistent variation or tendency was encountered in their series. Removal of the pituitary body in the rabbit results in a slight decrease in serum amylase activity, in contrast to the increase encountered in the hypophysectomized dog. The significance of the difference in behavior of the serum amylase system of the dog and of the rabbit in relation to the loss of hormones of the anterior lobe of the pituitary body and adrenal cortex is discussed. It is suggested that the various hormones which influence the serum amylase system do so indirectly. The conclusion is drawn that those endocrine glands which are intimately related to carbohydrate metabolism affect the serum amylase system.

Thompson,[55] in studying the relation of the anterior lobe of the pituitary body to the metabolism of acetone bodies, found that the role of the pituitary body in carbohydrate metabolism (as related to diabetes mellitus) is not clear. He stated:

> I should prefer to suppose as a working hypothesis that pituitary hormone or hormones promote processes of gluconeogenesis accompanied by acetone formation: either from glycerol and fatty acids of fats, respectively, or from sugar forming and acetone forming amino acids, or both; that hypophysectomy thus lessens the supply of new carbohydrate in the fasting or in the diabetic animal, and simultaneously decreases the likelihood of acetonuria; that the acetone bodies may be so produced more rapidly than they can be destroyed, whereas this will hardly be true of the sugar unless insulin is lacking; and that the pituitary either acts through the adrenal cortex or requires the presence of a cortical hormone in the circulation in order to exert its own direct control of gluconeogenesis effectively.

Shipley and Long [45] discussed the preparation of an extract which has a definite ketogenic activity. This extract did not affect the fed rat, but did affect the fasting rat. They concluded that the inhibitory action of anterior pituitary extract on the catabolism of carbohydrate and

55. Thompson, D. L.: The Anterior Pituitary and the Metabolism of Acetone Bodies, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:257-267, 1938.

protein offers satisfactory explanation for the ketosis that follows the injection. Gray [56] reviewed the results of previous workers concerning variations of ketonuria with respect to season, sex and pregnancy. When the high fat diet was administered, a greater ketogenic response was found in fasting male rats than in fasting female rats, whereas the increase in liver fats was greater in female rats. Evidence is presented that a large ketogenic response to administration of extract of the anterior lobe of the pituitary body is accompanied by a small increase in liver fat, and that the converse of this is also true.

Campbell [57] presented a method of assaying the potency of an extract of the anterior lobe of the pituitary body which increases the liver fat. Best and Campbell [58] described the effect of this extract on the liver fat in various animals. They studied the results both of fasting alone and of the administration of extract of the anterior pituitary lobe to fasting animals, and they determined urinary ketone bodies, liver fat and body fat. Fasting alone effected a pronounced increase in liver fat; there was an increase in the amount of liver fat following injection of the extract. An increase in the weight of the liver of the animals receiving injection was found to be referable chiefly to the deposition of water and fat. A slight increase in nonfatty solid material also occurred.

Houchin and Turner [59] studied the relation of the pituitary body to the blood lipids. They used rabbits as test animals. In one group they injected the extract intraperitoneally and found a gradual decline in the amount of blood lipids; the decline reached an average of about 36 per cent below the initial sample within six to eight hours and was followed by a return to approximately normal values after twenty-four hours. Similar results were obtained in a group of fasting rabbits. Using a pituitary extract which was rich in lactogenic hormone and in the hormone or hormones affecting carbohydrate metabolism as well as in the thyrotropic and the gonadotropic hormones, they found no influence on the lipids, nor was there any comparable effect following the injection of epinephrine, cortical extract or thyroxin. Thyroxin did begin to depress the blood fats after twenty-four hours. In a subsequent article, Houchin and Turner [60] outlined the method for assaying this hormone of fat metabolism.

56. Gray, C. H.: Determination of the Ketogenic Activity of Extracts of Endocrine Organs, Biochem. J. **32**:743-755 (April) 1938.

57. Campbell, J.: A Method of Assaying the Potency of Anterior Pituitary Extracts Which Increase Liver Fat, Endocrinology **23**:692-702 (Dec.) 1938.

58. Best, C. H., and Campbell, J.: The Effect of Anterior Pituitary Extracts on the Liver Fat of Various Animals, J. Physiol. **92**:91-110 (Feb. 16) 1938.

59. Houchin, O. B., and Turner, C. W.: The Relation of the Pituitary to Blood Lipids, Endocrinology **24**:638-644 (May) 1939.

60. Houchin, O. B., and Turner, C. W.: A Method of Assay for the Fat Metabolism Hormone of the Anterior Pituitary, Endocrinology **25**:216-220 (Aug.) 1939.

Neufeld and Collip [61] reported on a fraction prepared from the anterior lobe of the pituitary body which was demonstrated to have certain physiologic properties. They stated:

> Results reported herein indicate that there is obtainable from pituitary tissue a fraction which is thermostable within a wide range of *p*H. This fraction has been demonstrated to have the following physiological properties. *a*). Production of ketonemia in both normal and adrenalectomized rats. *b*). Production of increased glycosuria and ketonuria in the Houssay dog. *c*). An antagonistic action on the hypoglycemic action of insulin, and on the hyperglycemic action of adrenalin. *d*). A glycostatic action which has been demonstrated in rats, guinea pigs and rabbits.

Later, those authors (Neufeld and Collip [62]) discussed the effects of pituitary extract on ketonuria, fat content and fat distribution in the liver and tissues of mice.

Collip [63] has obtained an extract from the anterior lobe of the pituitary body which he said he considered to be the specific metabolic principle of the pituitary gland; on parenteral administration it causes an increase in the consumption of oxygen. He stated that this principle has been distinguished from most of the other well known principles, including the melanophore-expanding substance of the pars intermedia. The effect is produced almost immediately and has a relatively short duration. Rabinowitch and associates [64] discussed the influence of Collip's hormone on basal metabolism in man, following the work of O'Donovan and Collip.[65] Rabinowitch and co-workers expressed the opinion that this hormone appears to be independent of thyrotropic, adrenotropic and growth hormones and that although it is obtainable from the pars intermedia and the posterior lobe of the pituitary body, it is distinguishable from the pressor and oxytocic principles. Another report of this work has been published by Billingsley, O'Donovan and Collip,[66] in which they suggested a method for assaying this principle.

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61. Neufeld, A. H., and Collip, J. B.: Studies of the Effects of Pituitary Extracts on Carbohydrate and Fat Metabolism, Endocrinology **23**:735-746 (Dec.) 1938.

62. Neufeld, A. H., and Collip, J. B.: The Effect of Pituitary Extracts on Ketonuria, Fat Content and Fat Distribution in the Liver and Tissues of Mice, Endocrinology **25**:768-774 (Nov.) 1939.

63. Collip, J. B.: Results of Recent Studies on the Specific Metabolic Principle of the Pituitary Gland, Tr. A. Am. Physicians **54**:302-303, 1939.

64. Rabinowitch, I. M.; Mountford, M.; O'Donovan, D. K., and Collip, J. B.: Influence of a Specific Hormone of the Pituitary on the Basal Metabolism in Man, Canad. M. A. J. **40**:105-107 (Feb.) 1939.

65. O'Donovan, D. K., and Collip, J. B.: The Specific Metabolic Principle of the Pituitary, and Its Relation to the Melanophore Hormone, Endocrinology **23**:718-734 (Dec.) 1938.

66. Billingsley, L. W.; O'Donovan, D. K., and Collip, J. B.: The Specific Metabolic Principle of the Pituitary, Endocrinology **24**:63-68 (Jan.) 1939.

Summary.—Evidence is reported to suggest that extracts of the anterior lobe of the pituitary body are responsible for the deposition of fat in the liver and are related to the production of ketone bodies. There is insufficient evidence which can be used as a basis for description of specific hormones for these effects. Moreover it cannot be said that there is any specific hormone responsible for protein metabolism; all that is known is that the pituitary body aids in protein synthesis. The status of a "specific metabolic hormone" is uncertain.

THYROTROPIC HORMONE

Selye[67] has reviewed the literature on the thyrotropic and the adrenotropic hormone published prior to 1938.

Uotila[68] has emphasized the role of the pituitary stalk in the regulation of the anterior lobe of the pituitary body with special reference to the thyrotropic hormone. After section of the pituitary stalk in rats, enough thyrotropic hormone is produced to keep the thyroid gland histologically normal under ordinary conditions. However, section of the stalk followed by exposure to cold prevents increased secretion of the thyrotropic hormone and hypertrophy of the thyroid gland, which normally occur in intact animals on exposure to cold. This negative effect is not the result of general pituitary insufficiency. Hence it follows that in animals exposed to prolonged cold the hypothalamus stimulates the secretion of thyrotropic hormone by impulses transmitted through the pituitary stalk. The role of the pituitary stalk in this regulation is more important than that of the cervical sympathetic nerves. After section of the pituitary stalk in rats, the testicles and seminal vesicles remain normal but the usual damaging effect of cold on spermatogenesis is abolished. Hence, the influence of temperature on the secretion of gonadotropic hormones must be, to a certain extent, under hypothalamic control. Section of the pituitary stalk does not significantly affect the growth of rats. The anterior lobe of the pituitary body appears to have a basic secretory rhythm which is independent of the pituitary stalk under ordinary conditions and which is largely under humoral influences. Nevertheless, available evidence indicates that the hypothalamus and pituitary stalk participate in the regulation of secretion by the anterior lobe of the pituitary body in specific adjustments to certain environmental situations. In the present experiments, for example, evidence was adduced to indicate the mediation of stimuli through the stalk on prolonged exposure of the animal to cold.

67. Selye, H.: The Thyrotropic and Adrenotropic Hormones, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:239-246, 1938.

68. Uotila, U. U.: On the Role of the Pituitary Stalk in the Regulation of the Anterior Pituitary, with Special Reference to the Thyrotropic Hormone, Endocrinology **25**:605-614 (Oct.) 1939.

Efforts have been made to assay the amount of thyrotropic hormone, and Smelser [69] has reported his method of utilizing chicks for such assay. The effect of injection of thyrotropic extract on the weight of the thyroid gland of the day old chick was studied and compared with the results of other methods of testing for this hormone. The thyroid gland of the chick is an exceedingly sensitive medium for testing for this material, reacting to one-tenth the amount required to affect the weight of the thyroid gland in the guinea pig. Weight of the thyroid gland in the chick increases with the amount of hormone injected over a wide range of doses, whereas weight of the thyroid gland in the guinea pig increases over a narrow range of doses. Response of the thyroid gland of the chick is consistent, significant values being obtainable with small groups. Administration of the total dose of thyrotropic extract in multiple injections greatly increases the response. Crude nonpituitary extracts and urine and blood serums do not affect weight of the thyroid gland in chicks. Weight of the thyroid gland of normal guinea pigs is exceedingly variable, even when considered in terms of body weight, thus requiring that animals used for assay be within a narrow weight range. Histologic response is elicited by amounts of extract too small to produce hypertrophy and is, therefore, the more sensitive test, although not so adaptable to quantitative assay. If it is desired to demonstrate small amounts of thyrotropic principle, both histologic structure and weight of the thyroid gland should be taken as criteria of an effect. A statistical treatment of data obtained at assay is advocated. Bergman and Turner [70] have compared methods of assay of thyroid glands in the guinea pig and in the chick and have found the male chick unit of thyrotropic hormone to be about a fourth the amount of the guinea pig unit. On an equal bodily basis the male chick is only slightly more sensitive than the guinea pig. In a related paper, Turner and Cupps [71] reported the use of the chick assay method to determine the amount of thyrotropic hormone in the pituitary body of the albino rat during growth, pregnancy and lactation. The concentration of the thyrotropic factor in the pituitary body of both sexes increased during the period of rapid growth. However, the pituitary bodies of the female rats contained only about 50 per cent as much hormone as those of the male rats during this period. In a comparison of all weight groups, it was

69. Smelser, G. K.: Chick Thyroid Responses as a Basis for Thyrotropic Hormone Assay, Endocrinology **23**:429-438 (Oct.) 1938.

70. Bergman, A. J., and Turner, C. W.: A Comparison of the Guinea Pig and Chick Thyroid in the Assay of the Thyrotropic Hormone, Endocrinology **24**:656-664 (May) 1939.

71. Turner, C. W., and Cupps, P. T.: The Thyrotropic Hormone in the Pituitary of the Albino Rat During Growth, Pregnancy and Lactation, Endocrinology **24**:650-655 (May) 1939.

observed that the pituitary body of the female rat contained 62 per cent as much as the pituitary body of the male rat per gram of fresh tissue. In the estrous female rat the concentration of the hormone was low and continued so during the first half of pregnancy. There was evidence of a definite increase in the concentration of the hormone during the latter part of pregnancy and of an additional 40 per cent increase during lactation.

Jones [72] has studied the amount of thyrotropic hormone excreted in the urine by patients suffering from different conditions; he assayed the hormone by the chick assay method. Urine obtained from 2 patients who had myxedema, 1 who had postoperative hypothyroidism and 2 who had acromegaly was tested for thyrotropic activity; 1 specimen of urine (from a patient who had myxedema) gave results suggesting possible thyrotropic activity. Serums from 9 schizophrenic patients did not show any antithyrotropic activity when injected into chicks in association with known amounts of the thyrotropic substance.

Hundhausen [73] studied the effect of decreased intake of food on the thyroid gland and on the thyrotropic hormone of the anterior lobe of the pituitary body, and concluded that the changes which result (arrest of the activity of the thyroid gland and a decrease in the thyrotropic hormone of the pituitary body) are related to deficiency of vitamin B_1 rather than to limitation of intake of food, for rats maintained on a qualitatively adequate diet of half the usual amount do not exhibit these changes.

Canzanelli and Rapport [74] studied the effect of thyrotropic hormone alone and with other substances on the consumption of oxygen by the thyroid gland and the liver in vitro. They concluded that the action of the thyrotropic hormone on metabolism, through the thyroid gland, is not exerted by virtue of a specific effect on thyroxin, thyroglobulin or diodotyrosine. Thyrotropic hormone plus thyroid tissue after being incubated for four hours with guinea pig liver depressed the consumption of oxygen by the liver, as did thyroid tissue alone.

Merten and Hinsberg [75] studied the effect of ultrafiltrable and thyrotropic extracts of the anterior lobe of the pituitary body on carbohydrate

72. Jones, M. S.: A Study of Thyrotropic Hormone in Clinical States, Endocrinology **24**:665-671 (May) 1939.

73. Hundhausen, G.: Ueber den Einfluss verminderter Nahrungszufuhr auf Schilddrüse und thyreotropes Hormon des Hypophysenvorderlappens, Arch. f. exper. Path. u. Pharmakol. **192**:634-638, 1939.

74. Canzanelli, A., and Rapport, D.: The Effect of Thyrotropic Hormone, Alone and with Other Substances, on the In Vitro O_2 Consumption of Thyroid and Liver, Endocrinology **22**:73-79 (Jan.) 1938.

75. Merten, R., and Hinsberg, K.: Hypophysenvorderlappen und Kohlehydratstoffwechsel; Ueber die verschiedenartige Beeinflussung des Kohlehydratstoffwechsel durch Ultrafiltrate und Thyreotropwirksame Hypophysenvorderlappenextrakte, Klin. Wchnschr. **18**:901-905 (June 30) 1939.

metabolism. They found that the thyrotropic hormone is sensitive to heat and that it is not ultrafiltrable through filters impermeable to albumin. The hormone of the carbohydrate metabolism is ultrafiltrable and relatively thermostable. Ultrafiltrates of previously potent thyrotropic extract show no effect on the thyroid gland in guinea pigs.

Clinical Aspects.—Thompson and associates [76] reported the production of hyperthyroidism in man by the subcutaneous injection of an extract of the anterior lobe of the pituitary body. They were able to increase the metabolic rate from 20 to 30 per cent above normal and to produce all the symptoms of hyperthyroidism, including an increase in the size of the thyroid gland. When this extract was injected into patients suffering from exophthalmic goiter, there was an increase in both the signs and the symptoms of this disease. The effect was only temporary, and with continued treatment the basal metabolic rate decreased, sometimes to less than the original figure. No response occurred in patients suffering from total myxedema. There was an increase in the basal metabolic rate in patients who had moderate hypothyroidism (but with functioning thyroid tissue). This is further evidence of the fact that the thyrotropic hormone is dependent on a functioning thyroid gland for its activity. These observations were also made by Sharpey-Schafer and Schrire.[77]

Harrison [78] used thyrotropic hormone for 5 patients and studied its effect on blood cholesterol. The value for cholesterol was reduced in 2 patients who had low basal metabolic rates without myxedema, in 1 who had questionable myxedema and in 1 who had true myxedema. It did not cause any reduction in the value for blood cholesterol in another patient with true myxedema.

Emerson and Cutting [79] have attempted to assay the amount of thyrotropic hormone contained in the urine. Urinary thyrotropic activity could not be demonstrated in normal human beings or in normal animals, and could be demonstrated only rarely in human beings with hyperthyroidism. Transient urinary thyrotropic activity regularly followed thyroidectomy in animals and man, but could be demonstrated

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76. Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III, and Dickie, L. F. N.: The Production of Hyperthyroidism in Man with Pituitary Extracts, Tr. A. Am. Physicians **53**:243-244, 1938; Influence of Pituitary in Thyroid Disease, West. J. Surg. **47**:4-9 (Jan.) 1939.

77. Sharpey-Schafer, E. P., and Schrire, I.: The Effect of Pituitary Thyrotropic Extract on Subjects with Low Basal Metabolic Rates, Quart. J. Med. **8**:195-208 (July) 1939.

78. Harrison, K. S.: Clinical Application of Thyreotropic Hormone, M. J. Australia **1**:681-686 (May 6) 1939.

79. Emerson, K., Jr., and Cutting, W. C.: Urinary Thyrotropic Hormone, Endocrinology **23**:439-445 (Oct.) 1938.

only rarely in the presence of spontaneous hypothyroidism. In a subsequent paper Cutting, Robson and Emerson [80] reported refractoriness arising from administration of pituitary thyrotropic extracts and stated that they had much less evidence of refractoriness arising from the flavianate method of preparation from fresh pituitary bodies.

Grumbrecht and Loeser [81] injected thyrotropic hormone into pregnant guinea pigs and thereby caused fetal deaths.

Murphy and associates [82] reported hypertrophy of the heart and kidneys following the injection of thyrotropic hormone. This action was enhanced by "dye-blocking" the reticuloendothelial tissues previous to and during the period of injection.

Zeus [83] found definite evidence of cardiac dilatation, hypertrophy and degeneration of the heart in animals which had received similar injection (but without attention to the reticuloendothelial system).

Summary.—The thyrotropic hormone is one of the best established of all the pituitary hormones. The changes which occur in the thyroid gland following hypophysectomy are definite, as are those which can be produced by the experimental injection of an extract containing the hormone. There is ample clinical evidence to suggest the action of the pituitary body on the thyroid gland, as is often seen in the hyperthyroidism of acromegaly. The time may come when the thyrotropic hormone will be of clinical importance; the time is not yet.

ROLE OF THE ANTERIOR LOBE OF THE PITUITARY BODY WITH RESPECT TO THE MAMMARY GLAND

Riddle and Bates [84] commented on Kurzrock's report concerning the use of the lactogenic hormone in the treatment of women whose lactation was subnormal. They considered the term "lactogenic hormone" to be incorrect, since: (1) lactogenic activity is only one of the physiologic properties of the hormone; (2) it depresses the activity of the gonads by blocking the release of gonadotropic pituitary hormone; (3) it causes splanchnomegaly in some animals; (4) it has some effect on growth and probably has an action on functioning adrenal cortex; (5) it has

80. Cutting, W. C.; Robson, G. B., and Emerson, K., Jr.: Refractoriness from Pituitary Thyrotropic Extracts, Endocrinology **24**:739-740 (May) 1939.

81. Grumbrecht, P., and Loeser, A.: Fruchttod durch thyreotropes Hormon der Hypophyse, Klin. Wchnschr. **17**:233-235 (Feb. 12) 1938.

82. Murphy, R.; Lowther, S. W., and Pagniello, L.: Organ Hypertrophy Following Injections of Thyreotropic Hormone, Am. J. Physiol. **124**:110-113 (Oct.) 1938.

83. Zeus, L.: Ueber tierexperimentelle Herzbeeinflussung durch Verabfolgung von thyreotropem Hormon, Arch. f. Kreislaufforsch. **4**:49-68 (Feb.) 1939.

84. Riddle, O., and Bates, R. W.: Prolactin, A. Research Nerv. & Ment. Dis., Proc. **17**:287-297, 1938.

calorigenic action even in thyroidectomized animals, and (6) it probably shares in the diabetogenic response. Present extracts of this hormone are not free of intermedin hormones of the posterior lobe of the pituitary body, gonadotropic and thyrotropic hormones.

Folley [85] suggested that the term "prolactin" be reserved for the factor of the anterior lobe of the pituitary body that stimulates growth of the crop gland. He also wrote that the factor has not necessarily been shown to exert true lactogenic activity in mammals, and he pointed out that the circumstance that an extract of the pituitary body causes a few drops of fluid having the superficial appearance of milk to appear in rabbits or rats is not satisfactory evidence that the extract is truly lactogenic. He recalled previous work which indicates that the ability to stimulate lactation in cows is closely correlated with the glycotropic activities of the preparation rather than with the crop-stimulating activity. Folley and Young [86] studied the effect of anterior pituitary extract on established lactation in cows. They concluded that there is no evidence that a single lactation hormone is secreted by the anterior lobe of the pituitary body and suggested that the term be omitted from the literature. Folley [87] has likewise studied interactions of estrogen and prolactin with special reference to the effect of estrogen on the glandular response of the crop of the pigeon. He discussed the ability of estrogen to inhibit the crop-stimulating potency of this pituitary principle. Folley [88] has also reported a study of sex differences in the response of the crop glands of pigeons to prolactin and has obtained the most marked response in pigeons in which the gonads were undeveloped.

Li and his associates [89] presented evidence to indicate that primary amino groups are essential to the specific activity of the lactogenic hormone.

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85. Folley, S. J.: The Rôle of the Anterior Pituitary in Lactation: A Review of Recent Work, Lancet **2**:389-390 (Aug. 13) 1938.

86. Folley, S. J., and Young, F. G.: Effect of Anterior Pituitary Extract on Established Lactation in Cow, Proc. Roy. Soc., London, s.B **126**:45-76 (Sept. 23) 1938; Effect of Continued Treatment with Anterior Pituitary Extracts on Milk Volume and Milk-Fat Production in Lactating Cow, Biochem. J. **33**:192-197 (Feb.) 1939.

87. Folley, S. J.: Interactions of Estrone and Prolactin with Special Reference to the Effect of Estrone on the Pigeon Crop-Gland Response, Endocrinology **24**: 814-822 (June) 1939.

88. Folley, S. J.: Sex Difference in Response of the Pigeon Crop-Gland to Prolactin, Nature, London **144**:834 (Nov. 11) 1939.

89. Li, C. H.; Lyons, W. R.; Simpson, M. E., and Evans, H. M.: Essentiality of Primary Amino Groups for Specific Activity of the Lactogenic Hormone. Science **90**:376-377 (Oct. 20) 1939.

Turner and co-workers [90] have postulated evidence for the presence in the pituitary body of a mammary gland–stimulating factor not associated with the lactogenic hormone. This has been termed the "mammogenic hormone." They presented physiologic and chemical observations indicating the separate identity of this hormone and outlined a method for its assay.

Wiegand [91] and Ehrhardt and Voller [92] have reported observations on the influence of ovarian function on the lactogenic hormone. Reece and Mixner [93] studied the effect of testosterone on the pituitary body and the mammary glands. They reported that daily injections of testosterone in sexually mature spayed rats augmented the lactogenic content of the pituitary body by 40 per cent. These injections caused no change in the weight of pituitary bodies. They induced extensive development of the alveolar system of the mammary gland and initiated secretory activity. The authors concluded that the effect of testosterone is to stimulate the pituitary body to secrete and discharge the lactogenic hormone.

Lacassagne and Chamorro [94] subjected hypophysectomized male mice to weekly injections of crystallized estrogen. None showed any development of the mammary glands. Others received weekly injections of estradiol benzoate, starting a few days after birth of the animals. Two or three months later the breasts of these animals showed marked cystic hyperplasia. Hypophysectomy performed at this time produced rapid regression of breasts, which atrophied in a few weeks. Hypophysectomy performed on animals suffering from carcinoma of the breast produced temporary retardation in the growth of the tumor.

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90. Gomez, E. T., and Turner, C. W.: Further Evidence for a Mammogenic Hormone in the Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **37**:607-609 (Jan.) 1938. Lewis, A. A., and Turner, C. W.: Chemical Concentration of Mammogen from Prehypophyseal Tissue, ibid. **39**:435-436 (Dec.) 1938. Bergman, A. J.; Turner, C. W., and Cupps, P. T.: Are the Lactogenic and Carbohydrate Metabolism Hormones Identical? Endocrinology **23**:228-232 (Aug.) 1938. Lewis, A. A.; Turner, C. W.; Gomez, E. T., and Carroll, W. T.: The Biological Assay of the Mammogenic Duct Growth Factor of the Anterior Pituitary, ibid. **24**: 157-164 (Feb.) 1939.

91. Wiegand, M.: Ueber den Einfluss der Ovarialfunktion auf die laktogene Wirkung der Hypophyse, Arch. f. Gynäk. **165**:149-154, 1937.

92. Ehrhardt, K., and Voller, H. F.: Untersuchungen über das Laktationshormon des Hypophysenvorderlappens, Endocrinologie **22**:19-24 (July) 1939.

93. Reece, R. P., and Mixner, J. P.: Effect of Testosterone on Pituitary and Mammary Gland, Proc. Soc. Exper. Biol. & Med. **40**:66-67 (Jan.) 1939.

94. Lacassagne, A., and Chamorro, A.: Conséquences de l'hypophysectomie chez des souris sujettes au carcinome mammaire, traitées par hormone oestrogène, Compt. rend. Soc. de biol. **131**:1077-1078, 1939.

Clinical Aspects.—Ross [95] reported on the use of prolactin for lactating mothers when the secretion of breast milk on the fifth and the sixth postpartum day was less than 400 cc. He reported definite improvement in the condition of the patients as arising from the use of this hormone. Somewhat similar reports have been published by Stewart and Pratt [96] and by Kenny and associates.[97]

Werner [98] reviewed the clinical use of this hormone and reported the appearance of definite local reaction to the injection. He concluded that at present preparations of prolactin for clinical use are not sufficiently pure to warrant their use for human beings.

Beilly and Solomon [99] studied 108 cases in which they sought to inhibit lactation by means of administration of testosterone. Complete inhibition occurred in 58 per cent of the cases and incomplete inhibition in 40 per cent of the cases. Failure occurred in 2 per cent. Stephens [100] suppressed lactation in a female acromegalic patient by the administration of an estrogenic substance.

Summary.—The effects of extracts of the anterior lobe of the pituitary body on the mammary gland need critical consideration. The role of psychic influences on the secretion of breast milk, the presence of nutritional deficiences and perhaps other factors must be evaluated before it can be assumed that preparations of the anterior lobe exert true lactogenic action. There are as yet no preparations of the anterior lobe of the pituitary body with proved lactogenic action suitable for routine use for the human being.

EFFECT OF THE ANTERIOR LOBE OF THE PITUITARY BODY ON GROWTH PHENOMENA

There continues to be discussion regarding the actuality of a single growth hormone. Evans and his group [101] have submitted additional

95. Ross, J. R.: Prolactin: Its Effect on the Secretion of Woman's Milk, Endocrinology **22**:429-434 (April) 1938.

96. Stewart, H. L., Jr., and Pratt, J. P.: Effect of Prolactin on Mammary Gland Secretion, Endocrinology **25**:347-353 (Sept.) 1939.

97. Kenny, M.; King, E.; Evers, N., and Hurran, W. J.: Effect of Prolaction on Lactation in Nursing Women, with Notes on Preparation of Prolactin, Lancet **2**:828-831 (Oct. 14) 1939.

98. Werner, A. A.: Lactogenic Hormone: Severe Reactions from Its Use, Endocrinology **24**:119-121 (Jan.) 1939.

99. Beilly, J. S., and Solomon, S.: The Inhibition of Lactation Post-Partum with Testosterone Propionate, Endocrinology **26**:236-240 (Feb.) 1940.

100. Stephens, D. J.: Suppression of Lactation in Acromegaly During Estrogenic Therapy, Endocrinology **25**:638-641 (Oct.) 1939.

101. Evans, H. M.; Uyei, N.; Bartz, Q. R., and Simpson, M. E.: The Purification of the Anterior Pituitary Growth Hormone by Fractionation with Ammonium Sulfate, Endocrinology **22**:483-492 (April) 1938. Meamber, D. L.;

(Footnote continued on next page)

evidence to support their contention that the growth hormone is a specific hormone, and have reported that they have prepared a hormone free from lactogenic and thyrotropic effect. They have been able to promote growth in excess of the normal by injecting extract of the anterior lobe of the pituitary body in thyroidectomized animals, but the effect on growth is much greater when the thyroid gland is present. Thyroxin, of course, promotes the growth of thyroidectomized animals, but it does not have this effect when it is administered to thyroidectomized and hypophysectomized animals. Characteristic ovarian changes are found in animals which have been deprived of the thyroid glands for long periods, and these changes can be relieved by the administration of thyroxin but not by the injection of pituitary hormones. Salmon [102] implanted pituitary bodies in newborn thyroidectomized and parathyroidectomized rats after weaning time and failed to observe any response in growth in those animals in which thyroidectomy had been completed. The only observed response in growth occurred in those animals in which remnants of thyroid tissue were demonstrable.

Chou and associates [103] reported observations on the quantitative assay of the growth-promoting extract of the hypophysis. They noted a marked difference in response among the various sex and age groups. In percentile increase in weight, the sensitivity of the hypophysectomized rat is probably more than twice that of the normal adult female rat. Likewise, variation in size of the dose produces a clearer difference in response in the hypophysectomized rat. In the normal animal, unlike the effect in the hypophysectomized rat, a variation in dose of 100 per cent often fails to produce a convincing difference in response. The normal female rat is more sensitive than the normal male rat. In the series reported on by those authors, the response both of normal and of hypophysectomized rats after a rest period of two to six weeks was less if the extract had been given previously.

Lee [104] has studied the relation of the anterior lobe of the pituitary body to protein metabolism. He pointed out that the most characteristic

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Fraenkel-Conrat, H. L.; Simpson, M. E., and Evans, H. M.: The Preparation of Pituitary Growth Hormone Free from Lactogenic and Thyrotropic Hormones, Science **90**:19-20 (July 7) 1939. Evans, H. M.; Simpson, M. E., and Pencharz, R. I.: Relation Between the Growth Promoting Effects of the Pituitary and the Thyroid Hormone, Endocrinology **25**:175-182 (Aug.) 1939.

102. Salmon, T. N.: The Effect on the Growth Rate of Thyro-Parathyroidectomy in Newborn Rats and of the Subsequent Administration of Thyroid, Parathyroid and Anterior Hypophysis, Endocrinology **23**:446-457 (Oct.) 1938.

103. Chou, C.; Chang, C.; Chen, G., and Van Dyke, H. B.: Observations on the Quantitative Assay of Growth-Promoting Extract of the Hypophysis, Endocrinology **22**:322-334 (March) 1938.

104. Lee, M. O.: Relation of the Anterior Pituitary Growth Hormone to Protein Metabolism, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:193-221, 1938.

metabolic factor of growth in young animals is the active manufacture and deposition of body protein. There are a strongly positive nitrogen balance and a retention of water and minerals. This deposit and the growth process itself are similar, and both depend on the anabolic phases of amino acid metabolism. Lee said that "the growth hormone acts to create a plethora of protein deposition which allows a genetically limited process of conversion into permanent body structures to continue at its maximal youthful rate beyond the age at which it normally subsides, and causes a return toward that rate when such treatment is begun after chemical maturity has been reached." He also commented on the fact that in the fresh pituitary lobes of calves, steers and beeves, concentration of the growth hormone shows no appreciable difference; therefore he concluded that the amount of hormone needed is as great in adult animals as in young animals.

Clinical Aspects.—References to the treatment of pituitary dwarfism continue to appear.[105] The literature contains no report of any case of pituitary dwarfism in which the patient has achieved normal height by means of a pituitary hormone. Werner and associates[106] studied the treatment with growth hormones of children suffering from mongolism and found no evidence that injections of these factors caused any change in the patient's growth. Nothing new or important has been published concerning the diagnosis or treatment of acromegaly.

Summary.—There is no unquestioned evidence in support of the view that the pituitary body elaborates a pure growth hormone. Recognition of the fact that many glands (thyroid, gonads, pineal body and others) produce hormones which are concerned with the phenomenon of growth should not be neglected. Disturbances of growth are a part of the clinical syndrome produced by the hyperfunction or hypofunction of many glandular elements. Finally, the unsatisfactory results which have followed the clinical use of "growth hormone" should be considered.

105. Taylor, N. M.: Pituitary Dwarfism: Treatment with Growth Hormone, Endocrinology **22**:707-715 (June) 1938. Buchanan, J. A., and Ballweg, H. A.: A Case of Pituitary Dwarfism Treated with Antuitrin-G, ibid. **24**:565-571 (April) 1939. Lawrence, C. H., and Harrison, A.: Pituitary Dwarfism: Case Report Illustrating Response to Treatment, ibid. **23**:360-363 (Sept.) 1938. Beck, H. G., and Suter, G. M.: Pituitary Dwarfism with Diabetes Mellitus, ibid. **22**:115-119 (Jan.) 1938.

106. Werner, A. A.; Lewald, J.; Johns, G. A., and Kelling, D.: Growth in Children with Mongolism: A Four-Year Study of Eight Patients, Am. J. Dis. Child. **57**:554-563 (March) 1939.

EFFECTS OF THE ANTERIOR LOBE OF THE PITUITARY BODY ON THE ADRENAL GLANDS

Reese and associates [107] studied the histologic changes occurring in the anterior lobe of the pituitary body in the male rat following bilateral adrenalectomy. They found changes in all the cell types. The presence of a significant number of hyperactive basophilic cells suggested that an attempt is being made to compensate for the degenerative changes seen in other basophilic cells.

Swingle and fellow workers [108] injected extract of the anterior lobe of the pituitary body into adrenalectomized cats and increased the survival time, but this extract did not entirely substitute for the adrenal cortical hormone. The hormone of the corpus luteum ameliorates the symptoms of adrenal insufficiency in the dog, the ferret and the cat. Close similarity between progesterone and corticosterone probably explains the improvement which occurs in these animals in the presence of pseudopregnancy. Apparently the organism lacking adrenal tissue has the ability to convert progesterone into corticosterone. Swingle and associates concluded that it did not seem unreasonable to assume that the testes of cats contain progesterone and that the injection of extract of the anterior lobe of the pituitary body stimulates the gonad to produce excessive amounts, which in time are converted into corticosterone or related substances having activities similar to those of the cortical hormone. This opinion is supported by their observation that when extract of the anterior lobe of the pituitary body is injected into the normal cat, the health and survival time are much better than for similarly treated castrated cats. The fact that castrated cats react at all to injections of the extract of the anterior lobe of the pituitary body raises the question as to whether tissues other than gonads can form progesterone or related substances.

MacKay and Wick [109] studied the influence of adrenalectomy on the blood and urinary ketones during fasting and after administration of the extract of the anterior lobe of the pituitary body. They reported that adrenalectomy has little effect on the ketogenic activity of anterior pituitary extract.

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107. Reese, J. D.; Koneff, A. A., and Akimoto, M. B.: Anterior Pituitary Changes Following Adrenalectomy in the Rat, Anat. Rec. **75**:373-403 (Nov. 25) 1939.

108. Swingle, W. W.; Parkins, W. M.; Taylor, A. R.; Hays, W. H., and Morrell, J. A.: Effect of Extract of Anterior Pituitary upon the Life-Span of Castrate-Adrenalectomized Cats, Proc. Soc. Exper. Biol. & Med. **38**:876-879 (June) 1938.

109. MacKay, E. M., and Wick, A. N.: Influence of Adrenalectomy on the Blood and Urine Ketones During Fasting and Anterior Pituitary Extract Administration, Am. J. Physiol. **126**:753-757 (July) 1939.

Miller and Riddle [110] studied the effect of several pituitary hormones on adrenal cortical function. They said that the ability of pituitary extracts to stimulate cortical tissue is independent of their lactogenic, follicle-stimulating and thyrotropic potency. Androgen stimulated both the cortical and the medullary tissues in normal and in hypophysectomized pigeons. Estrogen stimulated the cortical tissue at least in the intact birds. Administration of thyroxin plus vitamin supplements elicited evidence of the ability of these substances to stimulate cortical tissues in hypophysectomized pigeons. Rosen and Marine [111] found the presence of the thyroid gland essential to the action of anterior pituitary extracts on the adrenal glands.

Ingle [112] studied the effect of administration of large amounts of extract of adrenal cortex on the adrenal cortices of normal and of hypophysectomized rats. He observed no apparent effect of the extract on the adrenal cortex and suggested support for the hypothesis that atrophy of the adrenal cortex may be referable to restriction of the output of the adrenotropic principle.

Martin and associates [113] recorded the excretion of an antidiuretic substance in the urine of adrenalectomized cats, a substance which is not present when adrenal cortical extract is administered. Sievert [114] described a substance obtained from the urine of 26 of 30 patients suffering from hypertension which when injected into mice was found to have an effect on the adrenal glands.

Rogoff and associates [115] presented additional evidence that the rate of secretion of epinephrine in the adrenal gland is not significantly altered by hypophysectomy.

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110. Miller, R. A., and Riddle, O.: Stimulation of Adrenal Cortex of Pigeons by Anterior Pituitary Hormones and by Their Secondary Products, Proc. Soc. Exper. Biol. & Med. **41**:518-522 (June) 1939.

111. Rosen, S. H., and Marine, D.: Inhibiting Effect of Thyroidectomy on Adrenal Cortex Hypertrophy Following Injections of Anterior Pituitary Extract, Proc. Soc. Exper. Biol. & Med. **41**:647-650 (June) 1939.

112. Ingle, D. J.: Effects of Administering Large Amounts of Cortin on Adrenal Cortices of Normal and Hypophysectomized Rats, Am. J. Physiol. **124**:369-371 (Nov.) 1938.

113. Martin, S. J.; Herrlich, H. C., and Fazekas, J. F.: Relation Between Electrolyte Imbalance and Excretion of Antidiuretic Substance in Adrenalectomized Cats, Am. J. Physiol. **127**:51-57 (Aug.) 1939.

114. Sievert, C.: Ueber den Reiztoff der genuinen Hypertension: III. Die Technik der Darstellung des blutdrucksteigernden Stoffes, seine physikalisch-chemischen Eigenschaften sowie der Nachweis der kortikotropen Substanz, Ztschr. f. klin. Med. **133**:261-276, 1938.

115. Rogoff, J. M.; Nixon, E. N.; Stewart, G. N., and Marcus, E.: Epinephrine Secretion in Hypophysectomized Dogs, Proc. Soc. Exper. Biol. & Med. **37**:715-717 (Jan.) 1938.

Summary.—There is a definite relation between the anterior lobe of the pituitary body and the adrenal cortex. Many of the functions of these two glands are rather similar. There is no pituitary "corticotropic hormone" which is suitable for human use.

GONADOTROPIC SUBSTANCES

Weil and Zondek [116] have studied the histologic aspects of the pituitary bodies of white rats into which estrogen has been injected. They injected large amounts of estrogen into these animals and found that marked enlargement of the anterior lobe of the pituitary body resulted; the enlargement varied directly according to the dose. All three types of pituitary cells became swollen, their Golgi apparatus was markedly dilated and most of the eosinophilic cells degenerated. This effect also varied directly with the dose. The pars intermedia and pars nervosa were not directly affected, but were compressed when the anterior lobe of the pituitary body was markedly enlarged. In advanced conditions, the pars nervosa exhibited a loss of cells and an increase in the glial fibers. Phelps, Ellison and Burch [117] studied the survival, structure and function of pituitary grafts in untreated rats and in rats into which estrogen had been injected. Results of the experiment, they said,

> indicate that some, if not all, of the effects of estrogen upon the structure of the anterior lobe can be produced in the absence of the nervous connections of the pituitary. They indicate further that the anterior lobe is capable of regenerating after having undergone partial degeneration. The observations on the effect of estrogen on the survival and regeneration of the grafts afford conclusive evidence that this hormone stimulates the pituitary.

Wolfe and Wright [118] studied the histologic effects induced in the anterior lobe of the pituitary body of the rat by the prolonged injection of estrogen, with particular reference to the production of pituitary adenomas. They studied the pituitary bodies of 37 rats which had received injections of estrogen for periods of from thirty to four hundred and twenty-five days. They found that in the rats treated for the shorter periods such injections induced marked but uniform hypertrophy of the

116. Weil, A., and Zondek, B.: The Histopathology of the Pituitary of the White Rat Injected with Follicular Hormone, Endocrinology **25**:114-122 (July) 1939.

117. Phelps, D.; Ellison, E. T., and Burch, J. C.: Survival, Structure and Function of Pituitary Grafts in Untreated Rats and in Rats Injected with Estrogen, Endocrinology **25**:227-235 (Aug.) 1939.

118. Wolfe, J. M., and Wright, A. W.: Histologic Effects Induced in the Anterior Pituitary of the Rat by Prolonged Injection of Estrin, with Particular Reference to the Production of Pituitary Adenomata, Endocrinology **23**:200-210 (Aug.) 1938.

pituitary body but that in rats receiving injections for a long time adenoma was induced. The initial reaction was generalized. The chromophilic cells were markedly degranulated and reduced in number, whereas chromophobes were decidedly increased in size and number. Three types of adenoma were described. These included: (1) pituitary adenomas, associated with profound vascular changes; (2) small nodular foci of cells presenting structural characteristics different from the cells of the surrounding extra-adenomatous tissue, and (3) diffuse adenomatous hyperplasia of the entire pituitary body. A vascular condition of the cells of the anterior lobe, considered to be degenerative, was described. Mitotic figures were generally more abundant in rats treated for shorter periods.

Ehrhardt and Funke [119] observed the action of the hormone of the corpus luteum on the anterior lobe of the pituitary body.

Collip, Selye and Williamson [120] found ovarian atrophy and signet ring cells in the hypophysis following the chronic injection of extract of the anterior lobe of the pituitary body.

Wolfe and Hamilton [121] studied the effect of testosterone propionate on the structure of the anterior lobe of the pituitary body of the female rat, with particular reference to the effects of prolonged administration on the numbers of cells. They found marked changes in the eosinophilic and basophilic cells.

Zondek [122] reported the development of enormous pituitary tumors following chronic injection of estrogenic substances into rats. The duration of treatment seemed far more influential on the development of the tumors than the amount of estrogen injected. The enlarged pituitary bodies and the tumors contained the same amount of gonadotropic hormone as did the normal pituitary bodies of control animals.

Friedgood and Dawson [123] reported on cytologic evidence of gonadotropic activity of the anterior lobe of the hypophysis in the rabbit. They

119. Ehrhardt, K., and Funke, R.: Untersuchungen über die Rückwirkung des Corpus luteum-Hormons auf den Hypophysenvorderlappen, Klin. Wchnschr. **17**:1588-1589 (Nov. 5) 1938.

120. Collip, J. B.; Selye, H., and Williamson, J. E.: Changes in the Hypophysis and the Ovaries of Rats Chronically Treated with an Anterior Pituitary Extract, Endocrinology **23**:279-284 (Sept.) 1938.

121. Wolfe, J. M., and Hamilton, J. B.: Action of Testosterone Propionate on the Structure of the Anterior Pituitary of the Female Rat with Particular Reference to the Effects of Prolonged Administration on the Levels of Cells, Endocrinology **25**:572-583 (Oct.) 1939.

122. Zondek, B.: Hypophyseal Tumors Induced by Estrogenic Hormone, Am. J. Cancer **33**:555-559 (Aug.) 1938.

123. Friedgood, H. B., and Dawson, A. B.: Cytologic Evidence of the Gonadotropic Activity of the Rabbit's Anterior Hypophysis, Endocrinology **22**:674-686 (June) 1938.

said that they found isolated small carmine-staining cells which occur in the anterior lobe of the pituitary body of castrated and immature rabbits. The number of these cells appears to be increased in animals approaching sexual maturity and may occasionally be fairly prominent in the pituitary body of the estrous rabbit. They dominate the cytologic appearance of the gland only after mating, during which period they become markedly enlarged and increased in number. The precise relation of this cell to the pituitary hormones which are known to be secreted is as yet not clear. Many difficulties remain; they exist because of the discrepancies in various species of animals, the various ages of animals studied and similar considerations.

Diaz and associates [124] studied the effect of various gonadotropic substances on the ovaries, pituitary body and adrenal glands of animals receiving long term injections of estrogen. Injections of estrogen produced a decrease in ovarian size, with general regression of the germinal and interstitial elements. Ovaries became atrophic but responded normally to injected gonadotropic substance. After long term injections of estrogen there was marked pituitary hypertrophy with no change in the adrenal glands. Therefore, the investigators said, they felt that estrogen acts directly on the pituitary body. The ovary is not fundamentally damaged, but becomes atrophic because of inadequate stimulation.

Lauson, Golden and Elmer Sevringhaus [125] studied the gonadotropic content of the hypophysis throughout the life cycle of normal female rats. They used the pituitary bodies from 248 donors varying in age from 14 days to 2½ years. The gonadotropic content was assayed by the uterine method on 22 day old immature rats. They found that pituitary potency rises to a peak at the age of 21 days and decreases gradually until the onset of puberty, at which stage there is a rapid decrease in potency to about half the prepuberal degree of potency. Throughout adult sex life, the content of the pituitary body in the preestrous stage remains constantly at the low prepuberal level despite continued increase in the size of the pituitary body itself. This is interpreted to mean that the pituitary body in the mature animal stores little of its gonadotropic complex, but rather releases it as rapidly as it is formed. Limited study of aged animals indicates that pituitary potency markedly increases as the ovaries fail. The assumed parallel between the natural and the artificial climacteric seems reasonably established.

124. Diaz, J. T.; Phelps, D.; Ellison, E. T., and Burch, J. C.: The Effects of Various Gonadotropic Substances upon the Ovaries, Pituitaries and Adrenals of Animals Receiving Long-Term Injections of Estrin, Am. J. Physiol. **121**: 794-799 (March) 1938.

125. Lauson, H. D.; Golden, J. B., and Sevringhaus, E. L.: The Gonadotropic Content of the Hypophysis Throughout the Life Cycle of the Normal Female Rat, Am. J. Physiol. **125**:396-404 (Feb.) 1939.

Makepeace [126] studied the effect of progestin on the anterior lobe of the pituitary body. He observed the changes which progestin produced in the endometrium from the proliferative to the progestational stage. He remarked that rabbits mate during pregnancy or pseudopregnancy but that they never ovulate after these matings, and he suggested that this circumstance arises because the functional corpus luteum secretes progestin, which prevents the discharge of the gonadotropic content of the pituitary body.

Bunster and Meyer [127] studied the effect of estrogen on the gonad-stimulating hormone of the anterior lobe of the pituitary body of castrated immature male and female rats in parabiosis with immature females. The data indicate that in the pituitary body of the castrated male rat a moderately higher gonad-stimulating activity develops than in that of the female rat. There is no qualitative difference in the sensitivity of the pituitary body of the two sexes to estrogen; the difference is quantitative only.

Lauson, Golden and Elmer Sevringhaus [128] observed the rate of increase in hypophysial gonadotropic content following ovariectomy in the rat, with observations on the weight of the hypophysis. They found that the increase in pituitary gonadotropic potency varied directly with the time that had elapsed since the animal was castrated.

Hamilton and Wolfe [129] injected synthetic androgenic substance (testosterone propionate) into rats and assayed the pituitary body for gonadotropic potency. They found that a marked lessening of gonadotropic potency resulted from the injection of androgen. The increase in gonadotropic capacity subsequent to castration (an increase which is augmented by the elapse of postcastration time) is largely, but not completely, negated by injection of androgen.

Chen and Van Dyke [130] studied the gonadotropic action of extract of the anterior lobe of the pituitary body after tryptic digestion and concluded that it abolished most of the luteinizing action of the majority

126. Makepeace, A. W.: The Effect of Progestin upon the Anterior Pituitary, Am. J. Obst. & Gynec. **37**:457-459 (March) 1939.

127. Bunster, E., and Meyer, R. K.: The Effect of Estrin on the Gonad-Stimulating Complex of the Anterior Pituitary of Parabiotic Rats, Endocrinology **23**:496-500 (Oct.) 1938.

128. Lauson, H. D.; Golden, J. B., and Sevringhaus, E. L.: The Rate of Increase in Hypophyseal Gonadotropic Content Following Ovariectomy in the Rat, with Observations on Gland Weights, Endocrinology **25**:47-51 (July) 1939.

129. Hamilton, J. B., and Wolfe, J. M.: The Effect of Synthetic Androgen upon the Gonadotropic Potency of the Anterior Pituitary, Endocrinology **22**: 360-365 (March) 1938.

130. Chen, G., and Van Dyke, H. B.: Gonadotropic Action of Anterior Pituitary Extract After Tryptic Digestion, Proc. Soc. Exper. Biol. & Med. **40**:172-176 (Feb.) 1939.

of the extracts. McShan and Meyer [131] expressed complete agreement with this observation. They studied the effect of extracts of both trypsin and ptyalin on the gonadotropic activity of pituitary extract and found, they said, that

> The luteinizing activity of extracts was largely, if not entirely, destroyed by trypsin, while it was relatively resistant to the action of the ptyalin preparations. On the other hand the follicle-stimulating activity was resistant to trypsin, while it was destroyed by the ptyalin preparations.

Abramowitz and Hisaw [132] reported that crystalline trypsin maintained at p_H 7.1 completely destroys follicle-stimulating hormones, luteinizing hormones and the urinary hormones of pregnancy. Breneman [133] reported augmentation of the pituitary gonadotropic hormone by chlorophyll, plant growth hormones and hemin. Friedman [134] reported extraction of the gonadotropic hormone from the leaves of young oat plants.

Friedman and Friedman [135] confirmed the results of R. T. Hill in finding the gonadotropic content of the pituitary body in the rabbit to be rapidly depleted within twenty-four hours after mating and in noting that restitution of the hormonal content of the pituitary body follows a characteristic curve during pseudopregnancy. They found the hormone content to be highest in the early spring and lowest in the early winter. Makepeace, Weinstein and Friedman [136] have confirmed this observation. Wells [137] has studied the fluctuation in the gonadotropic potency of 71 male ground squirrels. This potency varied markedly with the season and reached its highest point during the rutting period. Werner [138] has

131. McShan, W. H., and Meyer, R. K.: The Effect of Trypsin and Ptylin Preparations on the Gonadotropic Activity of Pituitary Extracts, J. Biol. Chem. **126**:361-365 (Nov.) 1938.

132. Abramowitz, A. A., and Hisaw, F. L.: The Effects of Proteolytic Enzymes on Purified Gonadotropic Hormones, Endocrinology **25**:633-637 (Oct.) 1939.

133. Breneman, W. R.: Augmentation of Pituitary Gonadotropic Hormone by Chlorophyll, Plant Growth Hormones and Hemin, Endocrinology **24**:488-493 (April) 1939.

134. Friedman, M. H.: Gonadotropic Extracts from the Leaves of Young Oat Plants, Proc. Soc. Exper. Biol. & Med. **37**:645-646 (Jan.) 1938.

135. Friedman, M. H., and Friedman, G. S.: Seasonal Variations in the Gonadotropic Hormone Content of the Rabbit Pituitary, Endocrinology **24**:626-630 (May) 1939.

136. Makepeace, A. W.; Weinstein, G. L., and Friedman, M. H.: Effect of Coitus on Gonadotropic Content of Pituitary Glands of Pseudopregnant Rabbits, Endocrinology **22**:667-668 (June) 1938.

137. Wells, L. J.: Gonadotropic Potency of the Hypophysis in a Wild Male Rodent with Annual Rut, Endocrinology **22**:588-594 (May) 1938.

138. Werner, S. C.: Failure of Gonadotropic Function of the Rat Hypophysis During Chronic Inanition, Proc. Soc. Exper. Biol. & Med. **41**:101-105 (May) 1939.

noted the failure of the gonadotropic function of the hypophysis in the rat during chronic inanition. He called attention to the similar findings which occur in human beings in such conditions as anorexia nervosa and marked loss in weight.

Fevold and Fiske [139] studied inhibition of the action of the follicle-stimulating hormone by the pituitary body. They were unable to separate this antagonistic principle from the luteinizing hormone. The authors concluded that the inhibiting agent is either the luteinizing hormone or a factor closely associated with and similar to it.

Foster and Fevold [140] discussed the relation of the two gonadotropic hormones in juvenile rabbits. The discussion regarding the number of gonadotropic hormones has continued. Saunders and Cole [141] stated:

> It is concluded from these experiments that, whereas it is possible to obtain from pituitary two gonadotropic extracts, having somewhat different effects, it is not certain that these are due to two separate hormones. Whether the ovarian response shall be follicle-stimulation or luteinization seems to depend to at least as great an extent on the manner of injection and state of the ovary as on the type of extract used. A new hypothesis is suggested as an alternative for the two-hormone theory.

Fevold [142] presented his evidence for concluding that the follicle-stimulating and the luteinizing hormone are separate.

Goss and Cole [143] have outlined their methods for the purification of the gonadotropic hormone of mares, which is by far the most potent hormone of this type yet available and the one which is being given an extensive clinical trial.

Jensen and associates [144] and Evans and co-workers [145] reported their conclusion that one of the gonadotropic hormones should be listed

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139. Fevold, H. L., and Fiske, V. M.: The Inhibition of the Action of the Follicle Stimulating Hormone by the Pituitary, Endocrinology **24**:823-828 (June) 1939.

140. Foster, M. A., and Fevold, H. L.: The Interrelationship of the Pituitary Gonadotropic Hormones in Follicular Development and Ovulation of the Juvenile Rabbit, Am. J. Physiol. **121**:625-632 (March) 1938.

141. Saunders, F. J., and Cole, H. H.: On the Reliability of Present Methods for Characterizing Two Gonadotropic Hormones, Follicle-Stimulator and Luteinizer, Endocrinology **23**:302-317 (Sept.) 1938.

142. Fevold, H. L.: Extraction and Standardization of Pituitary Follicle-Stimulating and Luteinizing Hormones, Endocrinology **24**:435-446 (April) 1939; Chemical Differences of Follicle-Stimulating and Luteinizing Hormones of Pituitary, J. Biol. Chem. **128**:83-92 (April) 1939.

143. Goss, H., and Cole, H. H.: Further Studies on the Purification of Mare Gonadotropic Hormone, Endocrinology **26**:244-249 (Feb.) 1940.

144. Jensen, H.; Simpson, M. E.; Tolksdorf, S., and Evans, H. M.: Chemical Fractionation of the Gonadotropic Factors Present in Sheep Pituitary, Endocrinology **25**:57-62 (July) 1939.

145. Evans, H. M.; Simpson, M. E.; Tolksdorf, S., and Jensen, H.: Biological Studies of the Gonadotropic Principles in Sheep Pituitary Substance, Endocrinology **25**:529-546 (Oct.) 1939.

as an "interstitial-cell stimulating hormone." The validity of this conclusion has not been confirmed.

Fluhmann [146] listed his evidence to justify the classification of gonadotropic substances into three groups: anterior pituitary, chorionic and equine gonadotropic hormones.

Greep [147] has studied the effect of gonadotropic hormones on the persisting corpora lutea in hypophysectomized rats. He utilized such rats to determine the cause of the persistence of corpora lutea, which, although nonfunctional, are at least morphologically wholly normal. The only substance which by itself will induce histologic involution has, paradoxically, been found to be luteinizing hormone, the same substance which under proper conditions acts as a stimulus for the formation of the corpora lutea. It is difficult at present to fit this observation into the current conceptions of the physiologic processes occurring in the normal reproductive cycle. Greep observed that when both follicle-stimulating and luteinizing hormones were administered simultaneously involution of the persistent corpora was remarkably rapid.

Bunde [148] injected certain gonadal and gonadotropic hormones into rats and observed their effects on the gestation period. Follicle-stimulating and luteinizing hormones injected during the latter part of pregnancy inhibited parturition. The fetuses were carried normally to term or beyond and in some instances were abnormally large. Unfractionated pituitary extract reacted in essentially the same way. The serum of pregnant mares was less effective in inhibiting parturition. Progestin had no inhibiting effect.

Friedgood [149] induced estrogenic behavior in anestrous rats with follicle-stimulating and luteinizing hormones of the anterior lobe of the pituitary body.

Foster [150] commented on the different response which is obtained by the injection of varying combinations of pituitary gonadotropic hormones into rabbits of different ages and in various physiologic states.

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146. Fluhmann, C. F.: Comparative Studies of Gonadotropic Hormones, Endocrinology **25**:193-198 (Aug.) 1939.

147. Greep, R. O.: The Effect of Gonadotropic Hormones on the Persisting Corpora Lutea in Hypophysectomized Rats, Endocrinology **23**:154-163 (Aug.) 1938.

148. Bunde, C. A.: The Effects of Certain Gonadal and Gonadotropic Hormones on the Gestation Period of the Rat, Endocrinology **23**:345-352 (Sept.) 1938.

149. Friedgood, H. B.: Induction of Estrous Behavior in Anestrous Cats with the Follicle-Stimulating and Luteinizing Hormones of the Anterior Pituitary Gland, Am. J. Physiol. **126**:229-233 (June) 1939.

150. Foster, M. A.: The Differential Action of Pituitary Gonadotropic Hormones upon the Secretory Capacity of the Graffian Follicle and Corpus Luteum, Am. J. Physiol. **121**:633-639 (March) 1938.

Robson [151] reported on the role of the gonadotropic hormones in the maintenance of luteal function. Results of his experiments suggest that in normal rats the anterior lobe of the pituitary body maintains luteal function not by the direct action of gonadotropic hormones on the corpus luteum but by stimulating the ovaries to secrete estrin, which in its turn acts on the corpus luteum. His work led him to pose the question of whether it is necessary to postulate the presence of the luteinizing hormone, since, according to his conclusion, luteal function is controlled by estrogen and the gonadotropic hormone has no direct action on the corpus luteum.

Hisaw, Fevold and Greep [152] have reviewed material on the gonadotropic hormones and described the effect of the follicle-stimulating hormone on the ovary, the different actions of the luteinizing hormone, the augmentation achieved when both are administered and the effects produced in the male.

Engle [153] has published an important review article on the gonadotropic substances of the blood, the urine and other body fluids.

Various methods of assaying gonadotropic hormones have been described. Friedman [154] concluded that the best test animal is the postpartum rabbit. D'Amour [155] considered the ovarian weight method preferable to that based on the formation of corpora lutea. Collip [156] has published a report on the third international conference at Geneva, which was to set international standards of pregnancy urine gonadotropin, mares' serum gonadotropin and certain hormones of the anterior lobe of the pituitary body. He stated:

> Although as yet only the standard of chorionic gonadotrophin is available, the writer has been informed that the standard for gonadotrophin of pregnant mares' serum will be ready for distribution within a few weeks, and that for prolactin shortly thereafter. It is to be hoped that as these standards become available all workers will avail themselves of them.

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151. Robson, J. M.: The Rôle of Gonadotropic Hormone in the Maintenance of Luteal Function, Quart. J. Exper. Physiol. **28**:49-59 (June) 1938.

152. Hisaw, F. L.; Fevold, H. L., and Greep, R. O.: The Pituitary Gonadotropic Hormones, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:247-256, 1938.

153. Engle, E. T.: Gonadotrope Stoffe in Blunt, Harn und in anderen Körperflüssigkeiten, Arch. f. Gynäk. **166**:131-167, 1938.

154. Friedman, M. H.: The Assay of Gonadotropic Extracts in the Postpartum Rabbit, Endocrinology **24**:617-625 (May) 1939.

155. D'Amour, M. C., and D'Amour, F. E.: The Assay of Gonad Stimulating Preparations, J. Pharmacol. & Exper. Therap. **62**:263-283 (March) 1938.

156. Collip, J. B.: International Standards for Pregnancy Urine Gonadotrophin, Mares' Serum Gonadotrophin and Certain Anterior Pituitary Hormones, Endocrinology **25**:318-324 (Aug.) 1939.

Frank and Berman [157] compared the four methods of bioassay for the gonadotropic factors and concluded that none of them can be considered better than roughly quantitative. They wrote as follows:

> A complete bioassay of the gonadotropic factors necessitates: (*a*) a concentration method which precipitates both follicle stimulating and luteinizing factors (acetone, acid alcohol methods), (*b*) ovarian 'values.' The following is suggested as the units: (*a*) the smallest amount of material which produces the full growth of 6 follicles, (*b*) the smallest amount of material which produces contiguous corpora lutea.
>
> Comparing the relative merits and disadvantages of these several procedures, we have decided to continue to use the ovarian values as our method for bioassay, because it appears to present a more comprehensive picture of the gonadotropic forces at work. We realize, however, that a more extensive statistical investigation of this problem is required in order to justify this choice for general adoption.

Rubenstein and Abarbanel [158] studied the effect of extracts of the anterior lobe of the pituitary body on spermatogenesis in rats and found that in normal immature male rats there was a premature descent of the testes with increased proliferative activity of the germ cell layer. The sperm cells showed no evidence of hastened maturation. Interstitial tissue was increased, and there was a precocious development of the epididymis to adult proportions. Injection of extracts of the anterior lobe of the pituitary body into normal mature rats caused a definite increase in the weight of the testes, moderate increase in the proliferation of the germinal epithelium and a moderate increase in tubular diameter.

Hoffman and Fouch [159] used a cutaneous test as an aid in the diagnosis of pregnancy. These results were not sufficiently reliable to secure acceptance of the method as a biologic test.

Page [160] did not find a markedly toxic substance in the blood of eclamptic patients, nor did he observe any evidence of hypersecretion of the posterior lobe of the pituitary body.

Greene [161] was able to induce in rabbits a disorder resembling the toxemia of pregnancy by the injection of an aqueous extract of the pituitary body of apes into rabbits at the twenty-seventh day of gestation.

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157. Frank, R. T., and Berman, R. L.: A Comparison of Four Methods of Bioassay for the Gonadotropic Factors, Endocrinology **25**:683-688 (Nov.) 1939.

158. Rubenstein, H. S., and Abarbanel, A. R.: Effect of Anterior Pituitary Extract on Spermatogenesis in Rat, J. Urol. **41**:773-779 (May) 1939.

159. Hoffman, P. E., and Fouch, F. L.: Results of Skin Tests for Pregnancy, Am. J. Obst. & Gynec. **35**:680-682 (April) 1938.

160. Page, E. W.: Effect of Eclamptic Blood upon Urinary Output and Blood Pressure of Human Recipients, J. Clin. Investigation **17**:207-218 (May) 1938.

161. Greene, H. S. N.: Experimental Induction of a Disorder Resembling Toxemia of Pregnancy in the Rabbit, Proc. Soc. Exper. Biol. & Med. **40**:606-608 (April) 1939.

D'Amour [162] reported qualitative studies of normal gonadotropic substances in the urine of normal women. He reported marked fluctuations in the hormonal content, depending on the stage of the menstrual cycle. He sought to determine how the gonadotropic substances in the urine of normal women were related to the menstrual cycle, and he compared the gonadotropin from the urine of normal menstruating women with the gonadotropic hormones of the anterior lobe of the pituitary body, of pregnancy urine, of menopausal urine and of pregnant mares' serum. On the basis of his and other observations he decided that the following could be used as a working hypothesis: The anterior lobe of the pituitary body stimulates and produces follicle-stimulating hormone; this maintains the normal growth of follicles; the follicles ripen and produce estrogen; estrogen acts on the anterior lobe of the pituitary body, causing production of the luteinizing hormone, and a combination of luteinizing hormone and follicle-stimulating hormone causes ovulation.

Fluhmann and Murphy [163] studied the content of the estrogenic and gonadotropic hormones of the blood of women at the climacteric and of castrated women and attempted to determine the possible relation of these hormones to the production and alleviation of symptoms associated with the cessation of ovarian function. They found that failing or absence of ovarian function is not associated with complete disappearance of substances having estrogenic properties when injected into spayed rodents. The hormone may be detected at cyclic intervals or it may be constant, but no relation between climacteric symptoms and absence or presence of the hormone could be established. A gonadotropic substance, probably originating in the anterior lobe of the pituitary gland, was found in excessive amounts in the blood of the female of climacteric age and after castration; it bears a distinct relation to the severity of the so-called climacteric symptoms.

Ascheim, Portes and Mayer [164] discussed the treatment with gonadotropic hormone of a variety of conditions, including hypophysial cachexia, amenorrhea, sterility, hemorrhagic syndromes, symptoms of hypophysial hyperfunction and others. This article is subject to the same criticism which can be leveled at others of its type—oversimplification of a complex subject and unjustified assumption that endocrinologic knowledge has reached the point at which physicians can intelligently prescribe for unintelligible situations.

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162. D'Amour, F. E.: A Qualitative Study of Normal Gonadotropin, Am. J. Physiol. **127**:649-653 (Nov.) 1939.

163. Fluhmann, C. F., and Murphy, K. M.: Estrogenic and Gonadotropic Hormones in Blood of Climacteric Women and Castrates, Am. J. Obst. & Gynec. **38**:778-785 (Nov.) 1939.

164. Ascheim, S.; Portes, L., and Mayer, M.: L'hormonothérapie hypophysaire gonadotrope, Ann. d'endocrinol. **1**:164-178 (May) 1939.

Johnston and Maroney [165] studied the nitrogen and calcium balances as affected by extracts containing growth and gonadotropic hormones administered for short periods to growing children. They wrote:

> A variety of responses followed—anabolic, katabolic and negative—which might be explained as being conditioned by *a*, the presence or absence of a hormonal defect; *b*, the state of the stores as judged by the control balance and *c*, the age of the child. Subjects included several girls with menstrual difficulties at puberty, 4 dwarfs—a cretin, an achondroplastic and 2 ateleotics, and a number of children who apparently had no endocrine abnormalities. Instances of complete loss of response in the nature of antihormone effect were encountered.

Boycott and Smiles [166] called attention to the fact that the diagnosis of hydatid mole by biologic assay of gonadotropic hormone alone is not reliable.

Grace [167] recorded the fallibility of the excretion of the follicle-stimulating gonadotropic hormone (prolan A) as a prognostic agent in instances of teratoma testis.

Moppett [168] reported that gonadotropic extracts of the anterior lobe of the pituitary body and extracts of growth hormone appeared to stimulate the growth of tumors in mice.

Turner [169] reported his results in the treatment of cryptorchidism with hormones of the anterior lobe of the pituitary body and similar hormones. He obtained descent in 14 of 26 cases, partial descent in 8 and failure in 4. The average length of treatment was twenty-five weeks; the average total dose was 13,000 rat units. There were no serious complications, but 1 boy had precocious secondary sexual development and another had softening of the testes after they had descended. Turner thought that treatment should be administered before the eighth year of the patient.

Dorff [170] reported on 12 boys with intra-abdominal cryptorchidism who were treated with gonadotropic substances. In 9 of these, the testes

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165. Johnston, J. A., and Maroney, J. W.: Observations on Nitrogen and Calcium Balances as Affected by Growth and Gonadotropic Hormones Administered for Short Periods to Growing Children, Endocrinology **25**:199-210 (Aug.) 1939.

166. Boycott, M., and Smiles, J. M.: Diagnosis of Hydatidiform Mole by Biological Assay, Lancet **1**:1428-1430 (June 24) 1939.

167. Grace, E. J.: Fallibility of Prolan A Excretion as Prognostic Agent in Cases of Teratoma Testis, Am. J. Surg **45**:280-281 (Aug.) 1939.

168. Moppett, W.: Substances Controlling the Growth of Implanted Tumours, M. J. Australia **2**:1065-1069 (Dec. 18) 1937.

169. Turner, H. H.: Anterior Pituitary Gonadotropic and Anterior Pituitary-Like Hormones in the Treatment of Cryptorchidism, South. M. J. **31**:381-387 (April) 1938.

170. Dorff, G. B.: Intra-Abdominal Cryptorchidism Treated with Gonadotropic Substance: Observations in a Series of Twelve Prepuberal Boys, J. A. M. A. **110**:1799-1802 (May 28) 1938.

descended to the inguinal canal. Dorff used the gonadotropic hormone of the urine of pregnant women. In 3 patients the testes came into the scrotum.

Bigler, Hardy and Scott [171] reviewed the literature and found the records of 191 patients who had been treated with the gonadotropic substances of the urine of pregnant women. Of these patients, 101 (52.8 per cent) were obese and 90 (47.2 per cent) had what is described as "a normal build." In 167 cases there was complete scrotal descent.

Bigler, Hardy and Scott [172] concluded that the best surgical repair of cryptorchidism followed preoperative treatment with gonadotropic substance from the urine of pregnant women (antuitrin-S). Postoperative treatment produced no beneficial effects. The best results were obtained when the boys were between 7 and 10 years of age.

Heckel [173] has published an excellent article on the treatment of sterility with gonadotropic and gonadotropic-like factors. He pointed out the many difficulties in the attempt to define the problems involved in any given case and the greater difficulties in the attempt to treat this condition. He reported that in some instances both gonadotropic principles and the extract of pregnancy urine appear to influence the number and viability of the spermatoza, but that in some patients the phenomena are only temporary. Heckel's figures on the induction of fertility were lower than those which other authors have reported. He called attention to the difficulty of determining just how much relation there is between the various endocrine glands and spermatogenesis.

Kunstadter [174] attempted to treat hypogenitalism in the male patient with serum of pregnant mares. He stated the following conclusion:

> It is believed that mares' serum is of definite value in the treatment of certain cases of hypogenitalism and cryptorchidism.
>
> As yet the optimal effective dose has not been established, but we believe that 50 to 100 U intramuscularly 3 times weekly probably will be more effective than the 10 to 20 U intramuscularly 3 times weekly administered to our patients. With the higher dosage results would probably be obtained in a shorter period of time.

171. Bigler, J. A.; Hardy, L. M., and Scott, H. V.: Gonadotropic Principles in the Treatment of Cryptorchidism: A Review of the Literature, Am. J. Dis. Child. **55**:100-111 (Jan.) 1938.

172. Bigler, J. A.; Hardy, L. M., and Scott, H. V.: Cryptorchidism Treated with Gonadotropic Preparations: III. Surgical Repair of Cryptorchidism With and Without Gonadotropic Therapy, Am. J. Dis. Child. **56**:989-996 (Nov.) 1938.

173. Heckel, N. J.: The Gonadotropic and the Gonadotropic-Like Factor in the Treatment of Male Sterility, Endocrinology **22**:111-114 (Jan.) 1938.

174. Kunstadter, R. H.: The Treatment of Hypogenitalism in the Male with the Gonadotropic Principle of Pregnant Mares' Serum, Endocrinology **25**:661-669 (Nov.) 1939.

From a clinical standpoint there is also great difference of opinion. Israel,[175] in concluding his article, stated:

> The treatment of dysfunctional menstrual disorders should be directed toward the primary site, usually the anterior hypophysis or the ovaries, of the derangement. Several therapeutic measures, each for a different purpose, may be required to restitute normal menstruation.
>
> Certain basic principles of organotherapy must be known before any of the currently employed therapeutic agents may be applied in an aberration of the menstrual function.

This concept is not shared by all workers in this field.

Fluhmann[176] carefully studied 19 patients who had dysmenorrhea. A series of 85 tests was conducted on these patients, and in 18 instances, the results failed to show any variation from the normal.

Sevringhaus[177] has discussed the treatment of menstrual disturbances, describing certain conditions in which, he said, he felt either ovarian or pituitary treatment offered advantages. He emphasized present difficulties of diagnosis and greater difficulties in treatment.

Hamblen[178] reported that a consideration of the results obtained in the treatment of anovulatory menometrorrhagia of functional character by gonadotropic principles seems to indicate that these principles have no claims for specificity and that symptomatic, ovarian or endometrium responses do not warrant the employment of those factors. Since the histologic aspects of functional amenorrhea of anovulatory type and those of so-called endocrine sterility are the same, similar assumptions seemed justified in these two instances. Hamblen[179] in a later article reviewed the literature and pointed out the various difficulties inherent in attempts to evaluate clinically ovarian responses to gonadotropic therapy. "Consideration of the clinical data available," he wrote, "indicates that there exists little definite proof that therapeutic efficiency has been established for the gonadotropes in most supposed endocrinopathic gynecology."

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175. Israel, S. L.: The Treatment of Dysfunctional Menstrual Disorders, Endocrinology **22**:253-261 (Feb.) 1938.

176. Fluhmann, C. F.: Endocrine Theories of Dysmenorrhea, Endocrinology **23**:393-397 (Oct.) 1938.

177. Sevringhaus, E. L.: The Choice of Ovarian or Pituitary Therapy for Menstrual Disturbances, Ann. Int. Med. **13**:629-635 (Oct.) 1939.

178. Hamblen, E. C.: Observations on the Clinical Employment of Pituitary and Pituitary-Like Gonadotropic Principles in Certain Conditions Characterized by Failure of Ovulation, Am. J. Surg. **41**:35-38 (July) 1938.

179. Hamblen, E. C.: The Clinical Evaluation of Ovarian Responses to Gonadotropic Therapy, Endocrinology **24**:848-865 (June) 1939.

Kobak [180] called attention to the danger of physicians' relying too much on the results of a laboratory test. He reported a case in which a woman had expelled a hydatid mole. Reactions to subsequent Friedman tests were positive, and it was assumed that the large uterus represented a recurrence of the mole. Abdominal hysterectomy was performed. The uterus was found to contain a normal fetus and placenta.

Schaefer, Sharp and Lammy [181] discussed in detail the use of gonadotropic substance from the urine of pregnant women in the treatment of 16 patients who had genital hypoplasia and cryptorchidism, 15 who had amenorrhea and 13 who had menometrorrhagia.

Schteingart [182] reported abnormalities of genital function and development among 70 per cent of sterile women. He listed the conditions as follows: (1) moderate genital hypoplasia to true infantilism in 80 per cent of the sterile women; (2) menstrual disturbances and amenorrhea in 40 per cent; (3) alterations of the sella turcica in 80 per cent; (4) obesity in 60 per cent, and (5) two disorders, (*a*) moderately lowered basal metabolism in many cases (but not characteristic) and (*b*) almost constantly lowered specific dynamic action. He also mentioned other less constant symptoms, such as deviations of stature and anomalies of the hair, including abnormal distribution, discrete hypotrichosis and advanced hirsutism.

Watson, Smith and Kurzrok [183] studied the relation of the menopause to gonadotropic hormones and concluded that the event is referable to a loss of response of the ovaries to gonadotropic hormones.

Campbell and Sevringhaus [184] said that hypofunction of the pituitary gland is responsible for amenorrhea, oligomenorrhea, menorrhagia, irregular cycles and sterility with anovulatory bleeding, and that these conditions are caused by a deficiency of the gonadotropic hormones and abnormalities in the timing of the liberation of these hormones. They concluded that in many instances polycystic ovaries are caused by long-continued stimulation of the pituitary body. For accurate diagnosis and conduct of treatment they advised endometrial biopsy, studies of vaginal epithelium and determinations of pregnandiol.

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180. Kobak, A. J.: The Interpretation of Excessive Gonadotropic Hormones Excreted in the Urine in Early Pregnancy, J. A. M. A. **110**:1179-1180 (April 9) 1938.

181. Schaefer, R. L.; Sharp, E. A., and Lammy, J. V.: Clinical Indications for Anterior Pituitary-Like Sex Hormone, Endocrinology **22**:643-662 (June) 1938.

182. Schteingart, M.: El factor hipofisario en la esterilidad, Prensa méd. argent. **25**:901-905 (May 11) 1938.

183. Watson, B. P.; Smith, P. E., and Kurzrok, R.: Relation of Pituitary Gland to Menopause, Am. J. Obst. & Gynec. **36**:562-570 (Oct.) 1938.

184. Campbell, R. E., and Sevringhaus, E. L.: Pituitary Gonadotropic Extracts for the Treatment of Amenorrhea, Menorrhagia and Sterility, Am. J. Obst. & Gynec. **37**:913-928 (June) 1939.

Murphy and Fluhmann [185] studied the relation of estrogenic and gonadotropic hormones to climacteric symptoms. They stated:

> The onset of the climacteric period is not associated with the disappearance of estrogen from the circulating blood.
>
> There is a relationship between the onset and severity of vasomotor symptoms and the presence of increased gonadotropic hormone in the blood. . . . Albright, Frank et al., . . . and others have shown that with the administration of large doses of estrogen an amelioration of symptoms occurs and the hormone disappears from the urine.

Fluhmann [186] has discussed the biologic differences between sex hormones of the anterior lobe of the pituitary body and gonadotropic substances from the urine of pregnant women. He obtained discouraging results in the treatment of amenorrhea with pituitary gonadotropic hormones and called attention to the use of the hormone of the urine of pregnant women for patients having profuse uterine hemorrhages with hyperplasia of the endometrium as well as for patients with undescended testes.

Summary.—Van Dyke [187] stated:

> If the number of articles published were acceptable as a safe basis of judgment, it could easily be concluded that the gonadotropic hormones are the most important secreted by the anterior pituitary. This field of inquiry is attractive not only because of its inherent importance but also because the probability of securing fruitful results is great. There can be no doubt that the anterior pituitary secretes gonadotropic hormone(s) essential for the normal functioning of the gonads of mammals and other vertebrates. As a result, nearly every investigator interested in the physiology of the gonads has quickly entered or wandered into the rich and diversified field of pituitary-gonad interrelationships—sometimes without realizing he is there. Furthermore, work may be greatly facilitated by the fact that the assay of the hormones with a fair degree of accuracy is often, but not always, easily accomplished.
>
> Despite all the labor represented by a vast number of reports during the past few years, it is not yet possible to enumerate satisfactorily the gonadotropic hormones of the pituitary. Separate follicle-stimulating and luteinizing hormones are generally believed to exist; it is by no means certain that the former specifically maintains the mammalian seminiferous tubules, whereas the latter insures the normal secretion of testicular hormone by the interstitial cells. It has been reported that principles synergizing with or antagonizing gonadotropic hormone have been extracted from the pituitary; however, their physiological importance is largely postulated from deduction. Several authors have recognized the great importance

185. Murphy, K. M., and Fluhmann, C. F.: The Relation of Estrogenic and Gonadotropic Hormones to Climacteric Symptoms, West. J. Surg. **46**:451-454 (Sept.) 1938.

186. Fluhmann, C. F.: Biologic Differences Between Anterior Pituitary Sex Hormone and Gonadotropic Substances from Pregnant Women, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:350-360, 1938.

187. Van Dyke, H. B.: The Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1938, vol. 2, pp. 47-48.

of excluding the animal's own pituitary in determining accurately qualitative and quantitative effects of extracts. The increased accuracy of interpretation more than justifies the great increase of labor required. Final judgment on the effect(s) of an extract should be based upon experiments with hypophysectomized animals.

The follicle-stimulating hormone often excreted in human urine in considerable amounts after spaying or castration or after the menopause probably originates in the anterior pituitary. On the other hand, the gonadotropic substances discussed in chapter iv appear not to be secreted by the hypophysis. These substances are prolan (from the chorionic cells of the human pregnant uterus), the gonadotropic hormone characteristic of pregnant-mare serum (likewise probably secreted by chorionic or endometrial cells), and the gonadotropic hormones of neoplasms such as hydatidiform mole, chorionepithelioma, and testicular tumor (from the cells of the neoplasms).

ANTIHORMONES

A. E. Severinghaus and Thompson [188] made a cytologic study of the hypophyses of 2 dogs and 2 sheep which had received prolonged injections of extracts of the pituitary glands of sheep, and of 2 dogs into which antihormone serum had been injected. They wrote:

The most important of the findings may be enumerated as follows: (1) The "Crooke changes" heretofore described only in the human pituitary gland have been experimentally produced in dogs, most prominently in the hypophyses of the dogs injected with the canine antihormone. (2) The changes in basophiles characteristic of both castration and thyroidectomy were observed in the hypophyses of the long-time injected dogs. (3) The presence of basophilic granules in the perivascular spaces and in the capillaries has been observed.

It is possible that the following reactions occurred in sequence during the course of prolonged injections of the sheep-pituitary extract: (1) An initial activation of the endocrine glands subsidiary to the pituitary gland occurred. In the sheep this process continued for the entire 6 months of injections. (2) The increased secretion of the subsidiary glands in turn activated the hypophyseal function. (3) The foreign protein linked to the injected sheep-extract gradually produced in the dogs a tissue and humoral resistance (antihormones), which ultimately inactivated the sheep-extract as well as certain pituitary hormones of the injected animal itself. (4) Thus, the antihormones produced a state of physiological hypophysectomy, which caused subsequent atrophy of the subsidiary glands. (5) The atrophy of the thyroid and gonads (and adrenals?) produced the final changes in the hypophyses characteristic of gonadectomy and thyroidectomy (and adrenalectomy?).

The Crooke changes characteristically found in the Cushing syndrome, associated with a diminished function of the gonads and thyroids, are believed to be related in some way to the effects of the inactivation of the subsidiary endocrine glands by the antihormone in these animals.[188b]

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188. Severinghaus, A. E., and Thompson, K. W.: (*a*) Production of Antihormones by Prolonged Administration of Pituitary Extract: Effect on Anterior Hypophysis, Proc. Soc. Exper. Biol. & Med. **40**:627-629 (April) 1939; (*b*) Cytological Changes Induced in Hypophysis by Prolonged Administration of Pituitary Extract, Am. J. Path. **15**:391-412 (July) 1939.

Werner [189] injected a beef pituitary substance containing thyrotropic hormone into 11 guinea pigs and found that refractoriness developed in 10 of these. A flavianate preparation made from the hypophysis of the same species, on the other hand, produced stimulation in 21 of 26 guinea pigs.

Rowlands and Young [190] found that antiserum produced by the injection of a crude pyridine extract of the anterior lobe of the pituitary body of the ox exhibits much greater antithyrotropic activity than antiserum obtained by the injection of physiologically equivalent amounts of a relatively purified thyrotropic preparation. Antiprolactin serum obtained by the daily injection of relatively pure prolactin containing no detectable thyrotropic hormone possessed definite antithyrotropic potency. Precipitin reactions between antithyrotropic serum and thyrotropic preparations were not found to be specific for the pituitary antigen This work was based on a previous study by Harington and Rowlands.[191]

Young [192] studied the production of antiserum to prolactin containing the glycotropic (anti-insulin) factor of the anterior lobe of the pituitary body. The serum of animals so treated for twelve weeks or more showed marked ability to prevent the hypertrophic response of the crop gland of the pigeon to prolactin. Rabbits which had received daily injections of prolactin for eighteen weeks showed a normal hypoglycemic response to insulin after the administration of a potent pituitary glycotropic preparation; that is, they were insensitive to glycotropic action of the extract. Bischoff and Lyons [193] were able to neutralize the crop gland–stimulating effect of beef and sheep mammatropin by injection into the pigeons of antimammatropic serum prepared in rabbits against either beef or sheep mammatropin.

Dohan and Lukens [194] studied the effectiveness of anithormones in the treatment of pancreatic diabetes. Two completely depancreatized dogs which received intraperitoneal injections of serum from a dog treated for more than nine months with extract of the anterior lobe of

189. Werner, S. C.: The Thyrotropic Hormone and the Antihormone Problem, Endocrinology **22**:291-301 (March) 1938.

190. Rowlands, I. W., and Young, F. G.: The Capacity of Pituitary Preparations Containing the Thyrotropic Hormone to Induce the Formation of Antisera, J. Physiol. **95**:410-419 (April) 1939.

191. Harington, C. R., and Rowlands, I. W.: Fractionation of Antithyrotropic and Anti-Gonadotropic Sera, Biochem. J. **31**:2049-2054 (Nov.) 1937.

192. Young, F. G.: The Production of Antisera to Preparations of Prolactin Containing the Glycotropic (Anti-Insulin) Factor of the Anterior Pituitary Gland, Biochem. J. **32**:656-664 (April) 1938.

193. Bischoff, H. W., and Lyons, W. R.: Immunologic Investigation of Hypophyseal Mammatropic Preparations, Endocrinology **25**:17-27 (July) 1939.

194. Dohan, F. C., and Lukens, F. D. W.: Antihormone Effects in Pancreatic Diabetes, Proc. Soc. Exper. Biol. & Med. **42**:167-171 (Oct.) 1939.

the pituitary body showed marked decrease in the amount of sugar in the urine. Two completely depancreatized dogs into which extract of the anterior lobe of the pituitary body was injected for thirty or more days showed after cessation of injections much less severe diabetes during fasting than had been present before injection. Metabolic behavior of these 4 dogs was much like that of depancreatized, hypophysectomized animals.

Zondek and associates [195] found that, according to their observations, the quantitative neutralization of "prolan" (the follicle-stimulating gonadotropic principle) and "antiprolan" follows strict laws, and they distinguished this reaction from fermentation reactions and from most of the immune reactions. Bunde and Hellbaum [196] studied the chemical and physical properties of gonadotropic antagonists.

Thompson [197] was able to interrupt the pregnancy of 12 dogs by the intravenous injection of a non-species-specific antigonadotropic canine serum. The action of the antiserum was comparable to that of physiologic hypophysectomy, and it may have been brought about by conferring on the dog a passive resistance (immunity) to its own pituitary gonadotropic hormone. Normal canine serum did not produce this effect. The antihormone did not cause any objective permanent ill effects in 3 dogs in which abortion had occurred, 2 of which later became pregnant and were again affected by abortion and 1 of which had a period of estrus. The aborted fetuses which were observed at delivery were alive, but subsequently died of prematurity and lack of maternal care. The antihormonal preparation used had no appreciable oxytocic activity when tested on the guinea pig uterus; it contained, however, a considerable amount of antidiuretic hormone, in addition to thyrotropic and gonadotropic antihormones. Kupperman and his associates [198] studied the effect of antigonadotropic serums on gonadotropic secretion in parabiotic rats. They reported:

> Anti-gonadotropic sera obtained from 2 adult, female rabbits receiving prolonged injections of an aqueous, supercentrifuged extract of sheep pituitary, inhibited the effectiveness of the endogenous gonadotropic secretion of the castrate partner's

195. Zondek, B.; Sulman, F., and Hochmann, A.: Relationship Between Inactivated Prolan and Antiprolan, Proc. Soc. Exper. Biol. & Med. **39**:283-287 (Nov.) 1938; The Antigonadotropic Factor: The Quantitative Aspects of the Prolan-Antiprolan Reaction, ibid. **40**:96-98 (Jan.) 1939.

196. Bunde, C. A., and Hellbaum, A. A.: Some Chemical and Physiological Properties of the Gonadotropic Antagonist, Am. J. Physiol. **125**:290-295 (Feb.) 1939.

197. Thompson, K. W.: The Termination of Pregnancy of Dogs by Gonadotropic Antihormone, Endocrinology **24**:613-616 (May) 1939.

198. Kupperman, H. S.; Meyer, R. K., and Hertz, R.: The Effect of Antigonadotropic Sera upon Gonadotropic Secretion in Parabiotic Rats, Endocrinology **24**:115-118 (Jan.) 1939.

pituitary in 11 female-female and 7 female-male parabiotics when injected into either the castrated or intact partner. The inhibitory sera was of sufficient titer to prevent the ovarian hypertrophy and the extensive luteinization found in the control series.

Katzman and associates [199] reported on an entirely different observation, namely, on a study of a progonadotropic serum of animals treated with hypophysial extracts. They found no evidence of antigonadotropic activity in the serums of sheep treated with chronic injection of extract of the pituitary body of sheep for as long as two hundred and sixty-two days. On the contrary, the serums continued to possess an enhancing action on the gonadotropic activity of this pituitary extract in immature female rats. The active factor of these serums also augments the action of rat pituitary extract, but not that of pig and beef pituitary bodies or that of the urine of pregnant and castrated women. When this factor is administered alone, it produces no apparent effect on the reproductive tracts of virgin female rabbits or of immature or mature female rats.

Dorff [200] studied 19 boys who had been treated for genital underdevelopment with gonadotropic substance from the urine of pregnant women. The tests showed no evidence of any antihormone. The lag or apparent halt in development in some of the patients treated was overcome by increases in dose or by a change to a different commercial brand of the same principle.

Summary.—The foregoing review emphasizes the unsettled state of knowledge regarding the question of the existence and entity of antihormones. Only one comment needs to be made. Until this question is settled, are clinicians justified in the extensive injection of pituitary hormones? Albright [201] is utilizing no anterior pituitary hormones in the treatment of patients in the Massachusetts General Hospital because of the possible harmful effects arising from the production of antihormones.

SIMMONDS' DISEASE

We consider Richardson's paper [202] to be one of the most important recent articles on the differential diagnosis of Simmonds' disease and anorexia nervosa. There have been reports of many cases of Simmonds' disease, most of which were really cases of anorexia nervosa. Richard-

199. Katzman, P. A.; Wade, N. J., and Doisy, E. A.: Progonadotropic Sera of Animals Treated with Hypophyseal Extracts, Endocrinology **25**:554-567 (Oct.) 1939.

200. Dorff, G. B.: Antihormone Studies in Boys Treated with Anterior Pituitary-Like Hormone for Genital Underdevelopment, Endocrinology **22**:669-673 (June) 1938.

201. Albright, F.: Personal communication to the authors.

202. Richardson, H. B.: Simmonds' Disease and Anorexia Nervosa, Arch. Int. Med. **63**:1-28 (Jan.) 1939.

son has performed a valuable service in illustrating the striking changes which can be produced by simple inanition and the splendid recovery which follows the simple ingestion of adequate quantities of a balanced diet. The photograph accompanying his article should be remembered by those inclined to publish "before and after" photographs illustrating the startling cures resulting from hormonal therapy.

Lisser and Escamilla [203] have published a critical statistical comparison of 69 verified and 134 unverified cases of Simmonds' disease. Their observations illustrate clearly the similarity of the findings in Simmonds' disease and those in anorexia nervosa. The fact that these authors could find only 69 verified cases of Simmonds' disease in the world literature again emphasizes the rarity of the condition.

Sheehan [204] has published an excellent review of Simmonds' disease referable to postpartum necrosis of the anterior lobe of the pituitary body. He stated that ischemic necrosis of the anterior lobe of the pituitary body is found relatively frequently among women who die in the puerperium, occurring in more than 25 per cent of such women. It is caused by severe hemorrhage or collapse of the patient at the time of delivery and begins at the time of these complications. Sheehan described the changes which occur in a person who has suffered from this condition. During the puerperium there is complete absence of lactation and sometimes hypoglycemia is present. The uterus becomes superinvoluted, the external genitals atrophy, menstruation does not return and libido is absent.

Hart and Lisa [205] reported a case of Simmonds' disease in which the diagnosis was confirmed at necropsy. Osgood [206] reported a case in which the same diagnosis was made and essentially the same findings were noted, but no explanation for this syndrome was discovered either during life or at necropsy. Dick and Dine [207] discussed the use of pituitary extract in cases of Simmonds' disease, but acknowledged the possibility that any conclusions based on such treatment may be subject to error. Kunstadter [208] discussed pituitary emaciation with improve-

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203. Lisser, H., and Escamilla, R. F.: Clinical Diagnosis of Simmonds' Disease (Hypophyseal Cachexia): Critical Statistical Comparison of Sixty-Nine Verified and One Hundred and Thirty-Four Unverified Cases, Tr. A. Am. Physicians **53**: 210-220, 1938.

204. Sheehan, H. L.: Simmonds' Disease Due to Post-Partum Necrosis of the Anterior Pituitary, Quart. J. Med. **8**:277-309 (Oct.) 1939.

205. Hart, J. F., and Lisa, J. R.: Pituitary Cachexia: Report of a Case, Endocrinology **25**:130-133 (July) 1939.

206. Osgood, E. E.: Pituitary Cachexia? Endocrinology **23**:656-660 (Nov.) 1938.

207. Dick, G. F., and Dine, W. C.: Pituitary Extract in Simmonds's Disease, Endocrinology **22**:703-706 (June) 1938.

208. Kunstadter, R. H.: Pituitary Emaciation, Endocrinology **22**:605-612 (May) 1938.

ment subsequent to endocrine therapy, but this report is subject to the same criticism mentioned by Dick and Dine. Bruckner and associates [209] and Davis [210] have reported cases of anorexia nervosa in which the clinical picture of Simmonds' disease was present. Foley and associates [211] reported an instance of tumor of the anterior lobe of the pituitary body associated with cachexia, hypoglycemia and duodenal ulcer. Brown and Eder,[212] and Effkemann and Müller-Jäger [213] reported the occurrence of Simmonds' disease following delivery. Seeger [214] reported a case in which a woman aged 62 died in shock shortly after appendectomy; for thirty years she had had the symptoms of Simmonds' disease and at necropsy was found to have marked atrophy of the anterior lobe of the pituitary body.

Straube's [215] report of the treatment of Simmonds' disease with extract of the posterior lobe of the pituitary body and adrenal cortical extract is open to doubt. This criticism applies also to Meyer's [216] treatment of Simmonds' disease by implantation of the pituitary body; Meyer reported dramatic improvement after the implantation of part of the pituitary body from a cat.

Bauer [217] has commented on the endocrine aspects of sprue and has emphasized the fact that many of the symptoms of this disease are similar to those reported on as associated with Simmonds' disease.

Summary.—Simmonds' disease is rare. Most of the patients reported as having Simmonds' disease are really suffering from anorexia nervosa.

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209. Bruckner, W. J.; Wies, C. H., and Lavietes, P. H.: Anorexia Nervosa and Pituitary Cachexia, Am. J. M. Sc. **196**:663-673 (Nov.) 1938.

210. Davis, H. P.: Anorexia Nervosa: A Case Report, Endocrinology **25**: 991-995 (Dec.) 1939.

211. Foley, M. P.; Snell, A. M., and Craig, W. McK.: Anterior Pituitary Tumor Associated with Cachexia, Hypoglycemia, and Duodenal Ulcer, Am. J. M. Sc. **198**:1-8 (July) 1939.

212. Brown, C. E., and Eder, L. F.: Acute Puerperal Hypophyseal Necrosis with Report of a Fatal Case, Am. J. M. Sc. **198**:166-171 (Aug.) 1939.

213. Effkemann, G., and Müller-Jäger, F.: Ueber das Auftreten von Hypophysenvorderlappen-Insuffizienzen nach starken Post-partum-Blutungen, Arch. f. Gynäk. **168**:867-872, 1939.

214. Seeger, E.: Akute hypophysäre Insuffizienz nach Appendektomie, München. med. Wchnschr. **86**:882 (June 9) 1939.

215. Straube, G.: Zur Therapie der Simmondsschen Krankheit, Klin. Wchnschr. **17**:1016-1017 (July 16) 1938.

216. Meyer, W. C.: Untersuchungen und Beobachtungen an Fällen von hypophysärer Magersucht (Simmonds) und deren Behandlung, insbesondere durch Hypophysenimplantation, Deutsches Arch. f. klin. Med. **182**:351-358, 1938.

217. Bauer, J.: Endocrine Aspects of Sprue: Their Relation to the Pituitary Syndrome in Anorexia Nervosa, J. Trop. Med. **42**:245-250 (Aug. 15) 1939.

CUSHING'S SYNDROME

Henderson [218] has reviewed the surgical results in 336 cases in which the patients were operated on by Harvey Cushing. In these, 260 of the lesions were chromophobic tumors (including 32 mixed adenomas), 67 were tumors of the acidophilic cells and 11 were adenocarcinomas. There was no example of a basophilic adenoma in this series.

Eisenhardt and Thompson [219] have reviewed the present status of so-called basophilism and have tabulated cases in which the diagnosis was verified. There have been 67 cases reported in the literature, with the incidence in sex approximately 2 females to 1 male. In 58 of these 67 cases (86 per cent) the tumor definitely was adenoma, and Eisenhardt and Thompson examined sections made in 39 of the 58 instances: in 33 the growth was true basophilic adenoma; in 2 it was chromophobic; in 2, mixed; in 1, a malignant tumor with metastasis, and in 1, unclassified. Excluded from consideration were the conglomerations of basophilic elements sometimes described as adenomas, but which so far as can be established have no clinical significance. The Crooke changes involving hyalinization of the cells were present in all these cases.

Maranon's [220] report showed that investigator's inclination to believe that the fundamental element in instances of Cushing's syndrome is hyperplasia of the adrenal glands. He stated that in many cases at the Pathologic Institute of Madrid basophilic adenomas have been found in instances of cardiac disease, renal disease, Parkinson's disease, cerebral hemorrhage and the like, without the least clinical sign of the presence of Cushing's syndrome. He reported 2 cases, in both of which not only the complete clinical picture of Cushing's syndrome but also tumors of the adrenal cortex were present, with no evidence of adenoma of the basophilic cells. Hall and his associates [221] reported a case of Cushing's syndrome in which they found no endocrine tumor of any sort. Sections of the pituitary body did show the Crooke changes. Ecker [222] studied the hyaline changes in the basophilic cells of the pituitary body obtained

218. Henderson, W. R.: The Pituitary Adenomata: A Follow-Up Study of the Surgical Results in Three Hundred and Thirty-Eight Cases (Dr. Harvey Cushing Series), Brit. J. Surg. **26**:811-921 (April) 1939.

219. Eisenhardt, L., and Thompson, K. W.: A Brief Consideration of the Present Status of So-Called Pituitary Basophilism with a Tabulation of Verified Cases, Yale J. Biol. & Med. **11**:507-522 (May) 1939.

220. Maranon, G.: Sur la pathogénie du syndrome de Cushing, Ann. d'endocrinol. **1**:241-256 (July) 1939.

221. Hall, G.; Kellett, C. E., and Stephenson, G. E.: Cushing's Syndrome: Report of a Case in Which No Endocrine Tumor Was Found, Lancet **1**:862-865 (April 15) 1939.

222. Ecker, A. D.: The Hyaline Change in the Basophil Cells of the Pituitary Body Not Associated with Basophilism, Endocrinology **23**:609-617 (Nov.) 1938.

from patients not suffering from Cushing's syndrome. He studied the anterior lobe of the pituitary body in a series of 721 cases. In 54 of these there were small basophilic adenomas. The hyaline change was found to be present to a marked extent in 8 of the pituitary bodies, an incidence of 1.1 per cent. However, the clinical and postmortem records revealed no evidence of Cushing's syndrome, even though in 1 case a basophilic adenoma (the cells of which, however, presented no evidence of hyalinization) also was present. In his summary Ecker wrote:

> The cells of the 54 basophil adenomas in this series, as well as of 18 others, representing a total of 72 adenomas previously found by Costello, were similarly examined. The hyaline change was present to a considerable degree in 4 cases (5.5 per cent). However, in these cases, there was neither hyalinization of the basophil cells outside of the adenomas nor any evidence of Cushing's syndrome in the clinical and post-mortem records. Finally, in none of the instances of hyalinization of the cytoplasm in the basophil cells in the 12 cases referred to were there such additional features as ballooning of the nucleus . . . , excessive vacuolization . . . , a tendency to multinucleation and general enlargement of the cells, which characterized the basophil cells of the pituitary body in 3 well-authenticated cases . . . of pituitary basophilism which were used as controls. It appears, therefore, unwarranted to consider hyalinization or degranulation of the basophil cells in the anterior lobe of the pituitary body of the human as invariably associated with the state designated as pituitary basophilism. Whether the hyaline change, when found together with the other cytologic features mentioned, will prove to be the "alteration of fundamental significance in the causation of this syndrome" . . . is an open question.

Anderson, Haymaker and Joseph [223] have continued their hormonal and electrolytic studies of patients who have Cushing's syndrome. They concluded that patients with that syndrome have in their blood an excess amount of a substance which resembles the adrenal cortical hormone and which has the ability to prolong the life of adrenalectomized rats. This substance is secreted in significant amounts by the kidney. They published a table comparing the electrolytes of the blood in the presence of Addison's disease and in the presence of Cushing's syndrome.

Crooke and Callow [224] discussed the diagnosis of Cushing's syndrome, particularly by means of the estimation of urinary androgens. They

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223. Anderson, E.; Haymaker, W., and Joseph, M.: Hormone and Electrolyte Studies of Patients with Hyperadrenocortical Syndrome (Cushing's Syndrome), Endocrinology **23**:398-402 (Oct.) 1938. Anderson, E., and Haymaker, W.: Adrenal Cortical Hormone (Cortin) in Blood and Urine of Patients with Cushing's Disease, Proc. Soc. Exper. Biol. & Med. **38**:610-613 (June) 1938. Haymaker, W., and Anderson, E.: The Syndrome Arising from Hyperfunction of the Adrenal Cortex: The Adrenogenital and Cushing's Syndromes—a Review, Internat. Clin. **4**:244-299 (Dec.) 1938.

224. Crooke, A. C., and Callow, R. K.: The Differential Diagnosis of Forms of Basophilism (Cushing Syndrome), Particularly by the Estimation of Urinary Androgens, Quart. J. Med. **8**:233-249 (July) 1939.

commented on the clinical difficulty involved in attempting to determine whether the condition is referable to tumor of the adrenal cortex or to a tumor of the basophilic cells of the pituitary body. They proceeded on the hypothesis that the level of urinary excretion of androgens or of closely allied compounds is an index of the activity of the adrenal cortex rather than of gonadal activity. In 1 case, in which an adrenal tumor was present, the urinary excretion of androgens was two or three times the normal amount; after removal of the tumor the value became subnormal, and within six months it had returned to a normal figure. In the second case, in which an adrenal tumor was present, the androgenic excretion was twenty times normal and later became thirty-five times normal. In the third case, in which an adrenal tumor was not found, the excretion was essentially within normal limits. In the fourth case, in which the patient was suffering from a basophilic adenoma, the androgenic excretion was below normal.

Cantarow [225] studied the concentration of chlorides in the urine of patients who had Cushing's syndrome. He employed the Cutler-Powers-Wilder test and found patients with Cushing's syndrome to be unable to eliminate chloride in the urine in as high a concentration as subjects with no apparent endocrine dysfunction. Cantarow called attention to the possible effect which the sex hormones may play in the urinary excretion of sodium, chloride and potassium, an effect which may be similar to that exerted by the adrenal cortical hormone.

Canelo and Lisser [226] reported a case of arrhenoblastoma in which Cushing's syndrome was simulated. The diagnosis was confirmed at necropsy, and no hyaline changes were found in the basophilic cells of the pituitary body. Elliott and Shallard [227] reported a case of tumor of the adrenal cortex in which Cushing's syndrome was simulated. Reuss, Sigmar and Roller [228] reported an instance in which Cushing's disease was treated with massive doses of estrogen. They concluded that this treatment resulted in the retention of calcium and phosphorus. The study was far from conclusive. Dunn [229] has reported improvement in the treatment of 11 women who had "a benign form of Cushing's syndrome" with the use of large doses of estrogen.

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225. Cantarow, A.: Urine Chloride Concentration in Patients with Cushing's Syndrome, Science **90**:375-376 (Oct. 20) 1939.

226. Canelo, C. K., and Lisser, H.: A Case of Arrhenoblastoma Which Simulated Cushing's Disease, Endocrinology **24**:838-847 (June) 1939.

227. Elliott, G. F., and Shallard, B. T.: Cushing's Syndrome, M. J. Australia **1**:390-393 (Feb. 26) 1938.

228. Reuss, L.; Sigmar, M., and Roller, D.: Mineralsalzbilanz bei einem Fall von M. Cushing und Versuch einer Behandlung mit hohen Follikulindosen, Wien. klin. Wchnschr. **52**:554-561 (June 9) 1939.

229. Dunn, C. W.: The Cushing Syndrome, Endocrinology **22**:374-385 (March) 1938.

Kehrer [230] has written a long article on the general subject of Cushing's syndrome, which is recorded here for the benefit of those who may be interested in Kehrer's purely hypothetic concept of the basis of the syndrome. He has attempted to localize the disturbed function to the midbrain but has presented no facts to support his hypothesis.

Summary.—The final word on the specific pathologic alterations which occur in the presence of Cushing's syndrome has not yet been spoken. Recent observations suggest that some of the effects of Cushing's syndrome may be mediated through the adrenal cortex. Certainly Kepler has proved that tumors of the adrenal cortex can cause a condition which duplicates the clinical picture of Cushing's syndrome. Additional study of urinary androgens of patients who have Cushing's syndrome, as well as additional observations on the exchange of electrolytes in such patients, ultimately may reveal the specific pathologic lesion (or lesions) in this disease.

POSTERIOR LOBE OF THE PITUITARY BODY AND DIABETES INSIPIDUS

Ranson, Fisher and Ingram [231] have reviewed the hypothalamic and hypophysial mechanism in diabetes insipidus. It is an accepted fact that diabetes insipidus is a result of a deficiency or an absence of the antidiuretic principles of the posterior lobe of the pituitary body. Lesions that interrupt the supraopticohypophysial tracts produce this disorder. Permanent diabetes insipidus results only if sufficient tissue of the anterior lobe of the hypophysis is left to maintain in animals or in man a fairly normal metabolic activity.

This last fact has been given particular emphasis by Richter.[232] Both Richter and Ranson agreed that the polyuria is primary to polydypsia. The maximal diuresis in diabetes insipidus is limited only by the maximal capacity of the kidneys.

Gersh [233] has studied the relation of the histologic structure to active substances extracted from the posterior lobe of the hypophysis.

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230. Kehrer, E.: Das Syndrom von Cushing, seine Analyse und Synthese, Ergebn. d. inn. Med. u. Kinderh. **55**:178-211, 1938.

231. Ranson, S. W.; Fisher, C., and Ingram, W. R.: The Hypothalamicohypophyseal Mechanism in Diabetes Insipidus, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:410-432, 1938.

232. Richter, C. P.: The Pituitary Gland in Relation to Water Exchange, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:392-409, 1938.

233. Gersh, I.: Relation of Histological Structure to the Active Substances Extracted from the Posterior Lobe of the Hypophysis, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:433-436, 1938.

Magoun and associates [234] have reported their results in the induction of diabetes insipidus in monkeys. They found that the animals could maintain a normal output of urine with the preservation of only a sixth to an eighth of the neurohypophysis, an observation comparable to the demonstrations of physiologic reserve reported for the other organs of the body, including the endocrine glands, by various workers. Magoun and co-workers concluded that the negative results encountered by other investigators in attempting to produce diabetes insipidus by low sections of the stalk are to be explained by the sizable amount of neurohypophysis left proximal to the section connected with the hypothalamus and innervated by the supraoptic nuclei.

Heinbecker and White [235] studied the effect of deprivation of water on dogs and found that the ability of these animals to concentrate urine was markedly reduced. The importance of this test in the diagnosis of diabetes insipidus in patients has been recently emphasized. Rutledge and Rynearson [236] and Keller [237] expressed disagreement with those who hold that the presence of the anterior lobe of the pituitary body is necessary to the production of permanent diabetes insipidus and reported diabetes insipidus in mature dogs studied for six months or longer after complete hypophysectomy.

Ranson and associates [238] were able to produce both adiposity and diabetes mellitus in the monkey within three weeks after lesions had been caused in the hypothalamus.

Hetherington [239] produced obesity in only 3 of 51 rats after the injection of chromic acid into the hypophysis. Histologic examination revealed that extensive damage had been done the hypothalami and hypophyses of the fat rats, whereas among the rats in which obesity was not produced hypothalamic injury was minor or absent, although hypophysial destruction was often severe. No instances of obesity among rats with intact hypophyses were discovered.

234. Magoun, H. W., and Ranson, S. W.: The Rôle of the Supraopticohypophysial Tract and the Neurohypophysis in the Regulation of Water Exchange in the Monkey, Tr. Am. Neurol. A. **65**:63-66, 1939. Magoun, H. W.; Fisher, C., and Ranson, S. W.: The Neurohypophysis and Water Exchange in the Monkey, Endocrinology **25**:161-174 (Aug.) 1939.

235. Heinbecker, P., and White, H. L.: The Rôle of the Pituitary Gland in Water Balance, Ann. Surg. **110**:1037-1049 (Dec.) 1939.

236. Rutledge, D. I., and Rynearson, E. H.: Diabetes Insipidus: II. Treatment by Insufflations of Powdered Posterior Pituitary Substance, Proc. Staff Meet., Mayo Clin. **14**:443-446 (July 12) 1939.

237. Keller, A. D.: Permanent Diabetes Insipidus Possible in the Absence of the Pars Anterior, Proc. Soc. Exper. Biol. & Med. **39**:555-557 (Dec.) 1938.

238. Ranson, S. W.; Fisher, C., and Ingram, W. R.: Adiposity and Diabetes Mellitus in a Monkey with Hypothalamic Lesions, Endocrinology **23**:175-181 (Aug.) 1938.

239. Hetherington, A. W.: Obesity in the Rat Following the Injection of Chromic Acid into the Hypophysis, Endocrinology **26**:264-268 (Feb.) 1940.

Swann [240] has studied the salt and water metabolism in induced diabetes insipidus in rats. On some rats he performed total nephrectomy, which prevented the polydypsia of both the transient and the permanent phase of the diabetes insipidus, provided the animals were drinking water. If they were drinking saline solution and had come to the permanent phase of diabetes insipidus, nephrectomy did not abolish polydypsia. Swann and Penner [241] reported marked aggravation in the symptoms of experimental diabetes insipidus by the administration of sodium chloride.

Swann and Johnson [242] studied the participation of the thyroid gland in diabetes insipidus and corroborated former observations regarding its importance in the exchange of fluids.

Neufeld and Collip [243] reported the existence of a substance in the posterior lobe of the pituitary body which is antagonistic to hyperglycemia caused by epinephrine. They concluded that it was not similar to the hormone that stimulates metabolism and that it was distinct from vasopressin and oxytocin.

Liu [244] studied pathologic lesions produced in the kidneys by the administration of the pressor principle of the posterior lobe of the pituitary body.

Necheles and Masur [245] produced a hemorrhagic condition of the entire gastrointestinal tract of dogs by the administration of acetylcholine and pitressin.

Elsom, Glenn and Drossner [246] commented on the stimulating effect which pitressin and amphetamine sulfate exert on the motor activity of the small intestine and the colon.

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240. Swann, H. G.: Some Experiments on Salt and Water Metabolism in Diabetes Insipidus, Endocrinology **25**:288-295 (Aug.) 1939.

241. Swann, H. G., and Penner, B. J.: The Effect of Salts on the Diabetes Insipidus Following Posthypophysectomy in the Rat, Endocrinology **24**:253-259 (Feb.) 1939.

242. Swann, H. G., and Johnson, P. E.: Thyroid Function in Diabetes Insipidus in the Rat, Endocrinology **24**:397-403 (March) 1939.

243. Neufeld, A. H., and Collip, J. B.: The Antagonist to Adrenalin Hyperglycaemia in Pituitary Extracts, Canad. M. A. J. **40**:537-539 (June) 1939; Further Studies on the Antagonist to Adrenalin Hyperglycemia in Pituitary Extracts, Endocrinology **25**:775-781 (Nov.) 1939.

244. Liu, S. H.: Pathological States Produced by Administration of Posterior Pituitary Pressor Principle, Chinese M. J. **55**:448-464 (May) 1939.

245. Necheles, H., and Masur, W.: Gastro-Intestinal Pathology in Dogs Following Administration of Acetylcholine and Pitressin, Am. J. Digest. Dis. **6**:389-391 (Aug.) 1939.

246. Elsom, K. A.; Glenn, P. M., and Drossner, J. L.: Intubation Studies of Human Small Intestine: XVIII. The Effect of Pitressin and of Amphetamine (Benzedrine) Sulphate on the Motor Activity of the Small Intestine and Colon, Am. J. Digest. Dis. **6**:593-597 (Nov.) 1939.

Shapiro [247] found that estradiol benzoate in large doses caused a significant decrease in the severity of diabetes insipidus. Because of the known antagonism between the estrogenic hormones and principles of the anterior lobe of the pituitary body, he received this reduction as evidence that there is a diuretic action of the anterior lobe.

Winter, Ingram and Gross [248] studied the effect of injections of pitressin on serum electrolytes and the exchange of water in cats with diabetes insipidus and adrenal insufficiency. They found that by the use of pitressin they could increase the survival time of adrenalectomized cats with experimentally induced diabetes insipidus, and they expressed the opinion that the increase in survival time was an expression of improvement in the ability of the animals to retain sodium and chloride.

Silvette and Britton [249] advanced the hypothesis that in the excretion of water and sodium by the kidney, the diuretic hormone of the adrenal cortex acts in physiologic antagonism to the antidiuretic hormone of the posterior lobe of the pituitary body. They said they considered the normal secretion of both of these hormones necessary to the proper maintenance of sodium chloride and water balance in the body.

In a later paper Corey, Silvette and Britton [250] presented additional observations to support this concept.

Wermer [251] postulated the existence of two types of diabetes insipidus —one caused by the absence of the antidiuretic hormone of the posterior lobe of the hypophysis and the other by an excessive amount of the diuretic hormone of the anterior lobe of the pituitary body.

Boyd and Whyte,[252] using frogs as the experimental animal, achieved results which caused them to believe that there are two principles involved in water balance, one causing retention of water and the other stimulating secretion of sodium chloride.

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247. Shapiro, B. G.: Control of Urinary Secretion by the Anterior Pituitary, Lancet **2**:1457-1460 (Dec. 24) 1938.

248. Winter, C. A.; Ingram, W. R., and Gross, E. G.: Effect of Pitressin Injections upon Serum Electrolytes and Water Exchange of Cats with Diabetes Insipidus and Adrenal Insufficiency, Am. J. Physiol. **127**:64-70 (Aug.) 1939.

249. Silvette, H., and Britton, S. W.: Renal Function in the Opossum and the Mechanism of Cortico-Adrenal and Post-Pituitary Action, Am. J. Physiol. **123**:630-639 (Sept.) 1938.

250. Corey, E. L.; Silvette, H., and Britton, S. W.: Hypophyseal and Adrenal Influence on Renal Function in the Rat, Am. J. Physiol. **125**:644-651 (April) 1939.

251. Wermer, P.: Hypophyse und Wasserhaushalt, Wien. Arch. f. inn. Med. **32**:189-214, 1938.

252. Boyd, E. M., and Whyte, D. W.: The Effect of Posterior Hypophyseal Extract on the Retention of Water and Salt Injected into Frogs, Am. J. Physiol. **125**:415-422 (March) 1939.

Pickford [253] reported the inhibitory effect of acetylcholine on water diuresis in dogs and found that this effect could not be obtained in the absence of the posterior lobe of the pituitary gland.

Necheles and Neuwelt [254] attacked this problem in a different way, for they were able by the injection of pitressin (but not pitocin) to prevent the effect of acetylcholine.

Kuschinsky and Bundschuh [255] wrote that in the posterior lobe of the hypophysis there is a substance having a diuretic effect, which in their opinion is entirely separate from the antidiuretic effect of pitressin and also differs from the effect of oxytocin. The oxytocic hormone has received additional study by Haterius and Ferguson [256] and by Stehle and Trister.[257]

Bundschuh and Kuschinsky [258] reported that after increased injection of sodium chloride the urine of rats contained active substances which resembled the vasopressor and the oxytocic principle. In the urine of normal human beings and rats only an oxytocic-like substance can be demonstrated.

Ingram and associates [259] found that normal cats subjected to conditions producing dehydration excrete appreciable quantities of an antidiuretic substance in the urine. Cats having diabetes insipidus referable to interruption of the supraopticohypophysial tract without direct injury to the pituitary body do not excrete this antidiuretic substance after dehydration. According to the observations of those investigators, when commercial preparations of the posterior lobe of the pituitary body are injected into normal cats and into cats with diabetes insipidus the antidiuretic substance appears in the urine in relatively small quantities. The results were interpreted as offering support for the suggestion of

253. Pickford, M.: The Inhibitory Effect of Acetylcholine on Water Diuresis in the Dog, and Its Pituitary Transmission, J. Physiol. **95**:226-238 (Feb. 14) 1939.

254. Necheles, H., and Neuwelt, F.: Antagonism Between Posterior Pituitary Secretion and Acetylcholine, Am. J. Physiol. **124**:142-148 (Oct.) 1938.

255. Kuschinsky, G., and Bundschuh, H. E.: Ueber die diuretische Wirkung von Hinterlappen-Präparaten und ihre Beziehung zur antidiuretischen Wirkung des Vasopressins, Klin. Wchnschr. **18**:207-208 (Feb. 11) 1939.

256. Haterius, H. O., and Ferguson, J. K. W.: Evidence for Hormonal Nature of Oxytocic Principle of Hypophysis, Am. J. Physiol. **124**:314-321 (Nov.) 1938.

257. Stehle, R. L., and Trister, S. M.: Additional Data Concerning the Chemistry of the Pressor and Oxytocic Hormones of the Pituitary Gland, J. Pharmacol. & Exper. Therap. **65**:343-352 (April) 1939.

258. Bundschuh, H. E., and Kuschinsky, G.: Ueber den Gehalt des Harnes an hinterlappenähnlichen Wirkstoffen, Klin. Wchnschr. **18**:251-252 (Feb. 18) 1939.

259. Ingram, W. R.; Ladd, L., and Benbow, J. T.: The Excretion of Antidiuretic Substances and Its Relation to the Hypothalamico-Hypophyseal System in Cats, Am. J. Physiol. **127**:544-551 (Oct.) 1939.

Goodman and Gilman, made in 1937, that the neurohypophysis may respond to the need for conservation of water by secreting increased amounts of diuretic substance, and as indicating that the supraopticohypophysial tract is necessary for this response.

Teel and Reid [260] studied the urine of patients suffering from preeclampsia and eclampsia and found a marked antidiuretic effect of concentrates of such urine.

Warkany and Mitchell [261] have reviewed the literature relating particularly to the clinical manifestations of diabetes insipidus. They emphasized the value of the urinary concentration test as a means of distinguishing true diabetes insipidus from nervous polyuria.

MacPherson [262] reported another instance of a patient who had both diabetes mellitus and diabetes insipidus. Postmortem examination showed slight enlargement of the anterior lobe of the hypophysis, with hyperplasia of eosinophilic cells.

Greene and Gibson [263] have recorded all the known cases of the coexistence of these two diseases. Rutledge and Rynearson [264] added a recent case.

Papers continue to be published indicating the existence of a possible relation of the posterior lobe of the pituitary body to widely separated conditions. Kramer, Grossman and Parker [265] advocated the intranasal use of solution of posterior pituitary of twice the U. S. P. concentration pituitrin (surgical) and of adrephine (a mixture of 1:10,000 solution of epinephrine hydrochloride and 2 per cent ephedrine sulfate, with 0.5 per cent chlorobutanol as preservative) as a protection against poliomyelitis.

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260. Teel, H. M., and Reid, D. E.: Observations upon the Occurrence of an Antidiuretic Substance in the Urine of Patients with Pre-Eclampsia and Eclampsia, Endocrinology **24**:297-310 (March) 1939.

261. Warkany, J., and Mitchell, A. G.: Diabetes Insipidus in Children: A Critical Review of Etiology, Diagnosis and Treatment, with Report of Four Cases, Am. J. Dis. Child. **57**:603-666 (March) 1939.

262. MacPherson, E.: Case of Diabetes Mellitus Associated with Lesions of the Pituitary Body, Glasgow M. J. **131**:220-224 (May) 1939.

263. Greene, J. A., and Gibson, R. B.: Coexistence of Diabetes Mellitus and Diabetes Insipidus: Report of a Case with Pregnancy, J. Lab. & Clin. Med. **24**:455-457 (Feb.) 1939.

264. Rutledge, D. I., and Rynearson, E. H.: Diabetes Insipidus: I. Coexistence of Diabetes Mellitus and Diabetes Insipidus, Proc. Staff Meet., Mayo Clin. **14**:441-443 (July 12) 1939.

265. Kramer, S. D.; Grossman, L. H., and Parker, G. C.: Evidence of Active Immunity to Experimental Poliomyelitis Obtained by the Intranasal Route in Macacus Rhesus, J. Exper. Med. **67**:529-544 (April) 1938.

Potter and Mueller [266] reviewed the use of pitressin in abdominal surgical procedures, reporting its routine use in 2,500 abdominal operations.

Metz and Lackey [267] treated with insufflations of posterior pituitary 42 patients who had peptic ulcer and reported satisfactory clinical results for 40 of them.

Metz [268] later reported the production of gastric lesions by the use of an extract of the posterior lobe of the pituitary body. The study was performed on rabbits, and far larger doses of the extract were given than were used in the treatment of patients. Portnoy [269] reported success in the treatment of herpes zoster with solution of posterior pituitary, either of U. S. P. concentration or of double strength. Cook and Stoesser [270] reported improvement in bronchial asthma with the use of this extract.

The method of administering preparations of the posterior lobe of the pituitary body is becoming variable. Many physicians employ hypodermic injection as the method of choice. Administration by intranasal insufflation of posterior pituitary powder is generally regarded as the best method, because it is effective, easy to use and inexpensive.

Court and Taylor [271] have prepared an emulsion with wool fat and beeswax as its base, which is injected subcutaneously, and they reported a desirable delayed absorption as produced by it. Wankmüller [272] outlined a method of intramuscular injection, also utilizing an emulsion. Von Matolay [273] transplanted half the pituitary body of a cat to the posterior part of the sheath of the rectus muscle and claimed a startling improvement.

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266. Potter, P. C., and Mueller, R. S.: The Value of Pitressin in Abdominal Surgery, with Special Reference to Dosage and Technique, Am. J. Surg. **43**:710-713 (March) 1939.

267. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Extract; Two Years' Experience, Texas State J. Med. **34**:214-220 (July) 1938.

268. Metz, M. H.: Gastric Lesion Produced by Posterior Pituitary Extract, Texas State J. Med. **34**:295-297 (Aug.) 1938.

269. Portnoy, S. H.: Some Experiences with Posterior Pituitary Solution in Herpes Zoster, J. Med. **18**:619-620 (Feb.) 1938.

270. Cook, M. M., and Stoesser, A. V.: Influence of Induced Variations in Electrolyte and Water Exchanges with Pitressin in Bronchial Asthma, Proc. Soc. Exper. Biol. & Med. **38**:636-638 (June) 1938.

271. Court, D., and Taylor, S. A.: Diabetes Insipidus: Treated by Slowly Acting Pituitary Emulsion, Proc. Roy. Soc. Med. **32**:1203-1206 (Aug.) 1939.

272. Wankmüller, R.: Ueber die Wirksamkeit eines Tonephindepots beim Diabetes Insipidus, Klin. Wchnschr. **18**:566-568 (April 22) 1939.

273. von Matolay, G.: Transplantationen von Kalbshypophysen bei Diabetes insipidus, Arch. f. klin. Chir. **191**:73-78, 1938.

Jones [274] described a new syndrome, which he considered to be, apparently, referable to overactivity of the posterior lobe of the pituitary body. He reported on patients suffering from hypertension, hypochromic anemia, achlorhydria (with histamine) and abnormal carbohydrate metabolism. He obtained from the urine of patients an extract which caused persistent elevation of blood pressure in the cat, the electrocardiographic tracings being essentially similar to those obtained from subjects affected by extract of the posterior lobe of the pituitary body. This extract from the patient's urine also had a pronounced antidiuretic action when it was injected into rats. The pressor action was unaffected by boiling; pitressin is likewise unaffected by boiling. The melanophore-dispersing action of the extract was demonstrated by the darkening obtained in frogs.

Summary.—Although the role of the posterior lobe of the pituitary body in the causation of diabetes insipidus is an accepted fact, the role of this lobe in the metabolism of water and sodium chloride is not entirely clear. Since the number of substances assigned to this lobe is increasing, the greatest caution in evaluating such observations is desirable. The exact origin of secretions assigned to the posterior lobe still needs to be clarified.

MISCELLANEOUS

Rasmussen's [275] report of the innervation of the hypophysis constitutes another of his classic studies. He found an enormous nerve supply to the posterior (neural) lobe, but noted that only a few nerve fibers pass through the intermediate region so that they reach slightly into the anterior lobe; the number is negligible. Such a large proportion of the anterior lobe appears to be devoid of nerve fibers that the existence of secretory nerves to this part of the hypophysis remains highly questionable.

Sutton and Brief [276] studied the cellular and physiologic changes in the anterior lobe of the hypophysis of rats deficient in vitamin A and found a significant increase in the basophilic cells in both sexes; the increase was greater in the male animals. The authors interpreted the results as indicating that deficiency of vitamin A produces a partial "castration effect" on the hypophysis. With vitamin A deficiency the content of gonadotropic hormone of the pituitary body is increased.

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274. Jones, E. I.: A New Syndrome Apparently Due to Over-Activity of the Posterior Pituitary, Lancet **1**:11-13 (Jan. 1) 1938.

275. Rasmussen, A. T.: Innervation of the Hypophysis, Endocrinology **23**: 263-278 (Sept.) 1938.

276. Sutton, T. S., and Brief, B. J.: Cellular Changes in the Anterior Hypophyses of Vitamin A-Deficient Rats, Endocrinology **23**:211-215 (Aug.) 1938; Physiological Changes in the Anterior Hypophysis of Vitamin A-Deficient Rats, ibid. **25**:302-307 (Aug.) 1939.

This increase in potency is greater in the male than in the female. Sure [277] observed the influence of avitaminosis on the weights of the endocrine glands. In vitamin A deficiency he found hypertrophy of the pancreas amounting to 40 per cent. In the presence of vitamin B_1 deficiency there is marked hypertrophy of the thyroid and adrenal glands, with decided atrophy of the thymus gland. Hypertrophy of the pituitary body was found in the presence of vitamin B_1 and vitamin G (B_2) deficiency to the extent of 40 and 25 per cent, respectively. Repeated depletions of vitamin B_1 have the following influence on weights of endocrine glands: The hypertrophy of the pituitary body entirely disappears, the thyroid gland is diminished to insignificant proportions and hypertrophy of the adrenal glands is reduced from 50 to 20 per cent.

Culmer and associates [278] reported depression of gastric secretion obtained by the gonadotropic fraction of urine obtained during pregnancy. It is concluded that this fraction contains a substance which suppresses the gastric secretory response of a dog to a test meal. The nature of the substance and its mechanism of action are problematic.

Plattener and Reed [279] observed muscular efficiency in rats into which anterior pituitary growth factor had been injected. In spite of their having greater average size, the animals which had received injections had no physiologic advantage over the untreated controls.

Ingle [280] studied the work performance of untreated hypophysectomized rats. There was a marked decrease in the capacity for work when total hypophysectomy had been performed. The study indicated that if half of the anterior lobe of the hypophysis is left intact the work performance of the rat is carried out at a nearly normal rate.

Rogers [281] has outlined another method for studying endocrine effects, utilizing observations of changes in the electrical potential during the estrous cycle. He concluded

> That hypophysectomy has the same effect on the electrical potential as ovariectomy and that, as in castrate animals, the normal estrous pattern of electrical

277. Sure, B.: Influence of Avitaminoses on Weights of Endocrine Glands, Endocrinology **23**:575-580 (Nov.) 1938.

278. Culmer, C. U.; Atkinson, A. J., and Ivy, A. C.: Depression of Gastric Secretion by the Anterior Pituitary-Like Fraction of Pregnancy Urine, Endocrinology **24**:631-637 (May) 1939.

279. Plattener, E. B.; Reed, C. I.; Brown, A. W., and Evans, H.: A Study of Muscular Efficiency in Rats Injected with Anterior Pituitary Growth Factor, Endocrinology **25**:401-404 (Sept.) 1939.

280. Ingle, D. J.: The Work Performance of Untreated Hypophysectomized Rats, Endocrinology **22**:465-468 (April) 1938.

281. Rogers, P. V.: Changes in Electrical Potential During the Estrous Cycle of the Rat: II. Partial and Complete Hypophysectomy and Pituitary Replacement Therapy, Endocrinology **22**:35-40 (Jan.) 1938.

potential may be reproduced by injections of theelin or prephysin; and also that as little as 0.5 per cent of anterior pituitary is sufficient to cause luteinization after the ovarian follicles have been matured with prephysin.

Cutting and Lewis [282] reported the failure of the anterior lobe of the pituitary body to produce hormones by the tissue culture technic.

Bischoff and Long [283] studied the endocrine factors influencing the development of tumors and concluded

> That the endogenous production of estrin and its related compounds by the ovary through prolan stimulation does not influence carcinogenesis, and that the production of carcinogenesis by massive doses of estrin (exogenous) may be without physiologic significance.

Twort and Lasnitzki [284] studied the weight of the pituitary body in rats inoculated with a transmissible tumor. They found that on the average the ratio of pituitary dry weight to brain weight was usually smaller in groups of animals having tumors than in those not having tumors. In most instances the relative weight of the pituitary body in the female animal was found to be greater than that in the male animal. Sittenfield [285] and Cramer and Horning [286] also have studied the relation between hormones and the growth of tumors.

Observations continue to be reported indicating the relation of seasons, hibernation, light and other factors to the endocrine glands. Foster and associates [287] attempted to induce hibernation but found that this could not be accomplished during the breeding season. There was a maximal tendency to hibernate, which persisted until the onset of genital enlargement. The studies of those investigators suggested that inactivity of the pituitary body is the primary factor responsible for the

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282. Cutting, W. C., and Lewis, M. R.: Failure of the Anterior Lobe of Pituitary to Produce Hormones in Tissue Culture, Arch. f. exper. Zellforsch. **21**:523-524, 1938.

283. Bischoff, F., and Long, M. L.: Endocrine Factors Influencing Tumor Development: The Effect of Prolan upon the Marsh-Buffalo Adenocarcinoma, Endocrinology **23**:327-329 (Sept.) 1938.

284. Twort, J. M., and Lasnitzki, M.: Studies on the Pituitary Weight of Rats Inoculated with a Transmissible Tumor, Endocrinology **23**:87-90 (July) 1938.

285. Sittenfield, M. J.: The Influence of the Anterior Lobe of the Pituitary on the Growth of Sarcoma and Carcinoma, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:466-470, 1938.

286. Cramer, W., and Horning, E. S.: The Prevention of Spontaneous Mammary Cancer in Mice by the Thyrotropic Hormone of the Pituitary Gland, Lancet **1**:72-76 (Jan. 8) 1938.

287. Foster, M. A.; Foster, R. C., and Meyer, R. K.: Hibernation and the Endocrines, Endocrinology **24**:603-612 (May) 1939.

phenomenon of hibernation. Bissonnette,[288] Riley and Witschi[289] and Benoit and Kehl[290] have observed the effect of light on the hypophysis and its hormones. Raab[291] has attempted to study the relation between light stimuli and metabolism of man. The eyes of the patients to be studied were taped for a period varying between seven and fifteen days. During this "black out," a marked decrease in blood sugar occurred. Other changes took place in the values for sugar tolerance and blood cholesterol and in the blood pressure and basal metabolic rate.

Képinov,[292] in studying the effect of insulin on epinephrine and in observing glycogenolysis in the liver of the frog as influenced by the administration of extracts of the anterior lobe of the pituitary body, has found that there is a marked difference from one season to another. His studies indicated that in frogs in the summer glycogenolysis occurs after a perfusion of the liver with insulin and Locke-Tyrode solution for twenty-five to thirty minutes, whereas in frogs in the winter four to five hours is required for this effect. Extracts of the anterior lobe of the pituitary body suppressed the antiglycogenolytic effects of insulin.

D'Amour and D'Amour[293] have assayed the potency of certain commercial hormone preparations. They concluded their paper as follows:

> The authors believe that the manufacturers of commercial hormone preparations are making an honest and sincere effort to produce dependable therapeutic agents. No one who is acquainted with the men connected with these organizations or who is familiar with the large amount of research which they have devoted to this problem could believe otherwise. At the same time, they themselves would no doubt be the last to assert that complete success had been achieved.
>
> In the light of the present study, we believe that two general criticisms are justified. Extracts of the anterior lobe, both gonadotropic and growth, and aqueous estrin preparations, appear to deteriorate on standing. This problem deserves study and if the time during which activity is retained can be determined it would be well to place an expiration date on the containers.

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288. Bissonnette, T. H.: Influence of Light on the Hypophysis: Effects of Long-Contained "Night-Lighting" on Hypophysectomized Female Ferrets and Those with Optic Nerves Cut, Endocrinology **22**:92-103 (Jan.) 1938.

289. Riley, G. M., and Witschi, E.: Comparative Effects of Light Stimulation and Administration of Gonadotropic Hormones on Female Sparrows, Endocrinology **23**:618-624 (Nov.) 1938.

290. Benoit, J., and Kehl, R.: Nouvelles recherches sur les voies nerveuses photoréceptrices et hypophysostimulantes chez le canard domestique, Compt. rend. Soc. de biol. **131**:89-93, 1939.

291. Raab, W.: Zur Frage: Licht und Stoffwechsel des Menschen, Ztschr. f. d. ges. exper. Med. **106**:154-166, 1939.

292. Képinov, L.: Nouvelles recherches sur l'action antiglycogénolytique de l'insuline. Suppression de l'effet antiglycogénolytique de l'insuline par l'extrait antéhypophysaire, Compt. rend. Soc. de biol. **128**:331-334, 1938.

293. D'Amour, F. E., and D'Amour, M. C.: The Potency of Certain Commercial Hormone Preparations, Endocrinology **22**:583-587 (May) 1938.

In the second place, the criticism of lack of uniformity in assay methods and units should be met. In the case of estrin, the Health Organization of the League of Nations has adopted a unit and, in time, official action regarding other hormones will probably be taken. In the meantime, however, to the non-commercial individual, at least, there appears to be no valid reason why the leading firms should not agree upon uniform methods of assay and upon standard units. Other industries have adopted rules of standard practice to which all members conform, with benefit to themselves and to the consumer.

Gaensbauer and Bradbury [294] have also assayed the comparative potency of products of the anterior lobe of the pituitary body. Bergman and associates [295] have discussed the efficiency of extraction and separation of certain hormones of the anterior lobe of the pituitary body. Saxton and Greene [296] observed the age and sex differences in the content of hormone in the hypophysis of the rabbit. Halpern [297] discussed quantitative cytologic studies on the anterior lobe of the hypophysis of fetuses and of children, correlated with sexual and skeletal development.

Sorsby, Avery and Cockayne [298] have reviewed the literature on the Laurence-Moon-Biedl syndrome. Boswell [299] reported the results of roentgen therapy administered to the pituitary and adrenal regions in the treatment of essential hypertension. In common with those of other reports of this type, the results are unconvincing. Waldorp and associates [300] reported the results of treatment of patients who displayed a variety of endocrine syndromes by the implantation of bovine pituitary bodies. He and his colleagues treated patients suffering from many conditions, from Simmonds' disease to alopecia, and, of course, reported improvement in most instances!

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294. Gaensbauer, F., and Bradbury, J. T.: Comparative Potency of Commercial Anterior Pituitary-Like Preparations, Endocrinology **24**:867-871 (June) 1939.

295. Bergman, A. J.; Houchin, O. B., and Turner, C. W.: Efficiency of Extraction and Separation of Certain AP Hormones, Endocrinology **25**:547-553 (Oct.) 1939.

296. Saxton, J. A., Jr., and Greene, H. S. N.: Age and Sex Difference in Hormone Content of the Rabbit Hypophysis, Endocrinology **24**:494-502 (April) 1939.

297. Halpern, S. R.: Quantitative Cytological Studies of the Anterior Lobe of the Hypophysis of Fetuses and Children, Correlated with Sexual and Skeletal Development, Endocrinology **22**:173-180 (Feb.) 1938.

298. Sorsby, A.; Avery, H., and Cockayne, E. A.: Obesity, Hypogenitalism, Mental Retardation, Polydactylia and Retinal Pigmentation (Laurence-Moon-Biedl Syndrome), Quart. J. Med. **8**:51-68 (Jan.) 1939.

299. Boswell, F. P.: Results of Roentgen Therapy in Essential Hypertension, Indust. Med. **7**:251-253 (May) 1938.

300. Waldorp, C. P.; Reforzo Membrives, J., and Luchetti, S. E.: Resultados personales de la implantación de hipófisis bovina en el ser humano, Prensa méd. argent. **26**:1179-1194 (June 21) 1939.

Maranon, Richet, Sourdel and Netter [301] discussed pigmentary disturbances of pituitary origin in human beings and presented the histories of 2 patients. One was a man who was struck on the right parietal region. He was unconscious for five or six hours. Diabetes insipidus developed, which responded to injections of solution of posterior pituitary. Later epileptic seizures occurred, and at this time a strange pigmentation appeared; it resembled vitiligo and appeared about twenty days after the accident. Five days later cranial decompression was performed, and within two weeks there was a slow but unmistakable decrease in the pigmentary disturbance. About two months after the accident the patient was able to return to work. The epileptic seizures had not returned at the time Maranon and his associates wrote, and the pigmentation had entirely disappeared. The second patient also had suffered fracture of the skull, with subsequent development of diabetes insipidus. Pigmentary disturbance likewise developed, which was described as a "melanoderma;" it was entirely different from that seen in the presence of any known disease and is described in detail in the article. These lesions did not disappear, but varied without any apparent relation to the changes in the other symptoms.

Teague [302] has studied the relation of the melanophore hormone of the pituitary body to the oxygen consumption of the rat. Hanes and Crew [303] discussed endocrinologic and metabolic observations made in cases of exfoliative dermatitis. Vollmer, Gordon, Levenstein and Charipper [304] studied the effects of hypophysectomy on the blood picture of the rat. Flaks, Himmel and Zotnik [305] recorded their evidence in favor of a hemopoietic hormone of the anterior lobe of the pituitary body.

Dohan, Jeffers and Creskoff [306] found that no increase in blood pressure, in erythrocytes, reticulocytes or hemoglobin was produced by the

301. Maranon, G.; Richet, C.; Sourdel, M., and Netter, H.: Les troubles pigmentaires d'origine hypophysaire en clinique humaine, Presse méd. **45**:1883-1885 (Dec. 29) 1937.

302. Teague, R. S.: The Relation of the Melanophore Hormone of the Pituitary Gland to Oxygen Consumption of the Rat, Endocrinology **25**:953-961 (Dec.) 1939.

303. Hanes, W. J., and Crew, R. S.: Endocrinologic and Metabolic Observations in Exfoliative Dermatitis, Endocrinology **24**:404-413 (March) 1939.

304. Vollmer, E. P.; Gordon, A. S.; Levenstein, I., and Charipper, H. A.: Effects of Hypophysectomy upon the Blood Picture of the Rat, Endocrinology **25**:970-977 (Dec.) 1939.

305. Flaks, J.; Himmel, I., and Zotnik, A.: La polyglobulie provoquée par les extraits de lobe antérieur d'hypophyse prouve l'existence d'une hormone hémopoiétique, Presse méd. **46**:1506-1509 (Oct. 12) 1938.

306. Dohan, F. C.; Jeffers, W. A., and Creskoff, A. J.: Blood Pressure and Hematology in Dogs Injected with Anterior Pituitary Extract, Proc. Soc. Exper. Biol. & Med. **39**:327-329 (Nov.) 1938.

repeated injection of an active saline extract of the anterior lobe of the pituitary body. Their reports did not confirm the assumption that excessive amounts of extract of the anterior lobe of the pituitary body may induce polycythemia. Sharp and Mack [307] discussed the relation of hemopoietic phenomena to endocrine disorders in women. The presentation is largely hypothetic. Snapper, Groen, Hunter and Witts [308] reported on 6 patients who had pituitary and gonadal insufficiency as well as associated achlorhydria, anemia and subacute combined degeneration of the spinal cord. Lawrence and Van Wagenen [309] reported on 5 patients who had tumors of the pituitary body and associated anemia. Wetzler-Ligeti and Wiesner [310] reported on the increased activity of the reticuloendothelial system following the injection of certain extracts of the anterior lobe of the pituitary body.

CONCLUSION

It must be apparent that in the years 1938 and 1939 no startling developments occurred which are likely to be of any value in treating patients during 1940. The aforementioned years have been valuable, however, in that efforts of workers in the "fundamental fields" continued to increase knowledge of the function of the anterior lobe of the pituitary body. Young's production of permanent diabetes mellitus is outstanding. It has been equally encouraging to note the growth of conservatism (and skepticism) in the minds of practicing physicians. Papers continue to appear recording the indiscriminate administration of unknown substances for the treatment of unknown conditions, but such publications are receiving less attention. The best papers are now recognized as being those which adhere to known fundamental principles and which manifest an interest in facts rather than in assumptions. Much that is written about the hypophysis is hypothesis.

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307. Sharp, E. A., and Mack, H. C.: The Relationship of Hemopoietic Phenomena to Endocrine Disorders in Women, Endocrinology **24**:202-218 (Feb.) 1939.

308. Snapper, I.; Groen, J.; Hunter, D., and Witts, L. J.: Achlorhydria, Anaemia and Subacute Combined Degeneration in Pituitary and Gonadal Insufficiency, Quart. J. Med. **6**:195-209 (April) 1937.

309. Lawrence, J. S., and Van Wagenen, W. P.: Hematopoietic Changes Associated with Pituitary Disease, Tr. A. Am. Physicians **53**:152-156, 1938.

310. Wetzler-Ligeti, C., and Wiesner, B. P.: Restropic Effects of Anterior Lobe Extracts, Endocrinology **22**:693-702 (June) 1938.

Book Reviews

Practical Bacteriology, Haematology and Animal Parasitology. By E. R. Stitt, M.D.; Paul W. Clough, M.D., and Mildred C. Clough, M.D. Ninth edition. Price $7.00. Pp. 961, with 208 illustrations. Philadelphia: P. Blakiston's Sons & Co., 1938.

Thirty years ago, Stitt published the first edition of "Bacteriology, Blood Work and Animal Parasitology," containing 245 pages and four plates. This edition received such universal support that the next year the second edition appeared, with 365 pages and 91 illustrations. Since that time there have been seven other editions, including the present. As these various editions give an accurate insight into the knowledge of the discussed subjects at the time, one may follow the progress of bacteriology, hematology and parasitology in the last three decades merely by reviewing the various editions in order.

The ninth edition is divided into four parts plus an appendix. Part 1 deals with bacteriology, considering first a classification of bacteria, with comments on the various methods of classification. Following this classification, the various bacteria are discussed with reference to the diseases they cause. Each discussion includes a description of the character of the lesion produced, the laboratory means of isolating and identifying the causative agents and serologic tests and other laboratory procedures used to identify the disease; and concluding each discussion is a short résumé of the treatment. One chapter deals with serologic methods, first defining the various terms used and then discussing various technics, with interpretation of the findings. In this chapter is found a discussion of anaphylaxis, hay fever and the complement fixation test. Of significance to both clinicians and clinical pathologists are the authors' suggestion for the conservative interpretation of the Wassermann reaction and the evaluation of the complement fixation and the various flocculation tests for syphilis.

Part 2 describes the various technics employed in hematology; then there follows a discussion of the interpretation of the hemogram with the prognostic indications of the leukocyte count. The anemias are classified according to cause, and each is described with special reference to the blood findings.

Part 3, after presenting a treatise on the classification of animal parasites, with a discussion of the nomenclature, offers a table which is useful to the investigator, as it outlines definite host, intermediate host, the reservoir of the virus and the transmission and pathogenicity of the protozoa, cestodes and nematodes. Also included is a discussion of the arthropodan diseases, with the life history and disease manifestations of each. Following this is a fuller description of the various protozoa and diseases produced. This part of the work is most elaborate and comprehensive.

In part 4 are considered the clinical and the pathologic examinations of the various fluids and organs of the body, including the examination of exudates from infectious processes found on and within the body for the purpose of determining the etiologic factors, and the routine examination of spinal fluid. The remainder of this section of the book deals with procedures common to clinicolaboratory medicine, including blood chemistry, urinalysis, renal function tests, gastric content analysis, examination of feces and basal metabolism and its relation to various endocrine disorders. The avitaminoses are considered. Each disease is discussed from the standpoint of the clinical picture presented, the pathologic changes, etiology and the laboratory procedures necessary to identify the disease; finally, there is a small paragraph on treatment of the various diseases discussed.

The appendix deals entirely with laboratory technic, confined to the care of instruments, sterilization and preparation of mediums and staining reagents.

This edition is characterized by the brief, concise and comprehensive way in which it is compiled. It should enjoy prestige to an even greater extent than the previous editions. It is heartily recommended as a text for students and as a reference text for both clinicians and laboratory workers.

Die Grundlagen der neuzeitlichen Ernährung des Deutschen Menschen: Ein Leitfaden für Studierende und Ärzte. By Dr. Ferdinand Bertram. Price, 5.80 marks, boards. Pp. 140. Leipzig: Georg Thieme, 1939.

The author of this manual, a recognized authority on diabetes, is physician in chief to the Second Medical Division of the Barnbeck General Hospital, Hamburg, and also professor of internal medicine.

The book includes a general review of the pathogenesis of hyperglycemia, glycosuria and acidosis, a discussion of the etiology, pathology and complications of diabetes and a detailed description of the author's therapeutic procedure. A very brief section is allotted to diabetes in children and another to prognosis. More attention to documentation would be appreciated. The bibliography is limited to a few monographs and less than a dozen general articles, mostly German.

The therapeutic procedure is sound for the most part. Exception may be taken to the objection of the author to having patients test their own urine. It is the opinion of leading American authorities on diabetes that the patient must keep himself continually informed on the state of his urine, in order to be able to regulate successfully the doses of insulin. Bertram states the belief that the sense of well-being of the patient provides a sufficient measure of safety for the adjustments of food and insulin and suggests that testing the urine may provoke "anticipation glycosuria." He makes a good point in demanding that the objective of treatment in diabetes must be to equip the patient for a practical life and not for the life of an invalid, and he believes that protamine zinc insulin is useful in attaining this objective.

In mild cases Bertram gives a single dose of "depot insulin" from the beginning of treatment. In cases of moderate and greater severity he first secures control by using four doses of unmodified insulin, giving one of these at 2 o'clock in the morning; then he substitutes "depot insulin" in two doses and finally attempts to give all the insulin required for the day in one dose. However, in a number of severe cases control with one dose of protamine zinc insulin a day has not been possible.

Among the complications attending treatment with insulin is a form of lipodystrophy, for which heretofore no satisfactory treatment has been found. Agreeing with other authors, Bertram believes that the disturbance is of nervous origin. Further evidence of this is supplied by one of his cases in which such atrophy of fat was successfully combated by giving large doses of thiamine chloride. Bertram also uses large doses of thiamine chloride in treating diabetic neuritis. He describes the results as being promptly favorable. (The reviewer has not had much success with this procedure and considers inconclusive the evidence that diabetic neuritis is often related to vitamin deficiency.)

The book contains much other comment of interest and deserves careful reading.

Architecture of the Kidney in Chronic Bright's Disease. By Jean Oliver. Price, $10. Pp. 256, with 112 illustrations. New York: Paul B. Hoeber, Inc., 1939.

Oliver has brought together his studies on the structure of the chronically diseased kidney. Many have been published previously in articles appearing since 1930 in the medical literature. The author correlates these numerous publications and adds data previously unpublished. The book is divided into eight chapters, the contents of which are suggested by the titles, which follow: Introduction, The Two Architectural Units of Chronic Bright's Disease, The Morphology of the Abnormal Nephron, The Aglomerular Nephrons of Terminal Bright's Dis-

case, The Transformation of the Arterial System in Terminal Bright's Disease, Factors Responsible for the Regressive Alterations of the Kidney Parenchyma in Bright's Disease, The Pattern of the Kidney in Bright's Disease and Epicrisis and Prolegomenon. The discussions are accompanied by fine illustrations, including excellent photomicrographs showing sections and nephron dissections of diseased kidneys. The dissections present the third dimensional aspect of the diseased renal parenchyma. This is particularly well presented and represents many tedious and careful dissections by the author and his assistants. By such means the entire renal functioning unit, the nephron, was isolated and the architectural derangement associated with a particular type of renal disease located and visualized in the third dimension. The dissections are not limited to the glomeruli and tubules of the nephron, but include also the vascular structures supplying it. These studies are especially interesting in connection with the vascular types of renal disease. The book is appended by twenty-three plates of a hundred and fifty-five figures of nephron dissections. These are briefly and well supplemented by legends which point out the anatomic abnormalities. There are also sixteen stereograms by which the reader may see these kidney structures in the third dimension.

The book is lucidly written and includes important necropsy material that has been collected and admirably correlated. The reviewer was impressed by the lack of sufficient correlation between the anatomic disturbances and physiologic changes encountered in Bright's disease. Although such a presentation was beyond the scope of the book, discussions of that nature would probably have increased its values. The book is recommended to all in the various fields of medicine but particularly to pathologists and internists who need to think of diseased structures, not only renal, in the third dimension.

Consolidated Indices. Compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society. Price $12.50. Pp. 451. Springfield, Ill.: Charles C. Thomas, Publisher, 1939.

The "Consolidated Indices" consists of a comprehensive index covering 160,000 references and 22,500 author references from the 30,000 pages of the four periodicals of the American Roentgen Ray Society. Under the chairmanship of Dr. Merrill C. Sosman, the publication committee, in collaboration with the editorial office, began early in 1936 to formulate plans for a complete subject and author index covering this entire group of publications. Dr. George H. Smith dealt with this mass of material. In the results of his compilation are seen a praiseworthy accomplishment.

In the "Indices" the transactions of the society, the original articles, the editorials and the biographic and historical sketches, together with the abstracts of both domestic and foreign journals, have been carefully and thoroughly indexed with regard both to subjects and to authors.

Included in this series, covering a period of approximately thirty-five years, are: the *Transactions of the American Roentgen Ray Society* for the years 1903 to 1908, inclusive; the *American Quarterly of Roentgenology,* which in some measure overlapped the *Transactions,* being issued during the interval from 1906 and 1907 to 1912 and 1913; the *American Journal of Roentgenology,* comprising nine consecutive volumes issued from 1913-1914 through 1922, and the *American Journal of Roentgenology and Radium Therapy,* volumes X to XXXVIII, inclusive, the last completing the year 1937.

Dr. Smith explains the variations in the system of pagination occurring in these several publications and the significant errata. He explains the arrangement and presentation of the author and subject index, facilitating its use.

This work is a special event in publishing in this field of medicine.

The American Roentgen Ray Society presents a subject and author index to the medical world covering all of its publications. The Consolidated Indices will

be appreciated by every one as a convenient comprehensive reference source to most of the world roentgenologic and radium literature published from 1903 to 1937 inclusive.

Die Diät-und Insulinbehandlung der Zuckerkrankheit. By Dr. Franz Depisch. Second edition. Price 4.80 marks. Pp. 155. Vienna: Julius Springer, 1939.

This treatise on the theory and treatment of diabetes is written for the German general practitioner. The second edition contains directions for the use of various types of long-acting insulins, such as protamine zinc insulin. The increasing incidence of diabetes has prompted the author to include a discussion of prevention; and since prevention can largely be effected by control of overweight, directions are given for reducing procedures.

The author regards diabetes as a disturbance of the normal balance between the activity of the islands of Langerhans and the opposing regulation of the blood sugar (*Gegenregulation*). The cause of diabetes in the great majority of cases, perhaps in all cases he says, depends on a certain functional insufficiency of the insular organ, but the clinical features of the individual case are determined not alone by the degree of insufficiency of the insular organ but also importantly by the associated state of activity of the opposing regulation.

For purposes of treatment, distinction is made between supportive management directed at the insufficiency of the islands of Langerhans and attempts to suppress the activity of the opposing regulation. The islands are spared by restricting the supply of sugar formers (carbohydrate and protein). This, however, depends on providing calories in the forms of fat which has the disadvantage, according to the author's view, of activating the opposing regulation. This disadvantage, as a rule, is balanced by the increasing capacity of the islands. The treatment directed at the opposing regulation involves the use of a liberal amount of carbohydrate and restriction of fat.

The book also contains much advice regarding the treatment of both the acute and the chronic complications of diabetes.

Etude morphologique et biologique sur les flagellés intestinaux parasites des murides: Etude comparative des flagellés du cobaye. By Léon Morenas. Price, 60 francs, paper. Pp. 234. Paris: Masson & Cie, 1938.

This is a report of a thorough investigation of the flagellated intestinal parasites of wild and tame rats and mice and of guinea pigs. In these animals in a wild state infestation is usually of a single strain, while laboratory stocks generally harbor several strains. Of the flagellates studied, only Giardia appears to be pathogenic; the others could be considered commensals. The biologic experiments are interesting. It is apparent that the character and the quantity of intestinal mucus are determining factors in the selection of the sites of infestation. A predominantly gram-positive intestinal bacterial flora is unfavorable for parasitism. The effect of the avitaminoses studied is surprising. Scorbutic guinea pigs are neither more nor less susceptible to parasitic infestation than normal animals. Animals suffering from A-avitaminosis, however, because of the diminished production of mucus, are much more resistant to parasitism than are normal animals.

Efforts to produce animal infestation with human flagellates were not successful and suggested that the organisms are species specific and further that these animals are probably not vectors. The study is well done and should be a useful addition to the library of parasitologists.